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(54) Title: ACYCLIC HYDRAZIDES AS CANNABINOID RECEPTOR MODULATORS

(57) Abstract: The acyclic hydrazides of the invention are antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. The compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders (including smoking cessation), the treatment of obesity or eating disorders, as well as the treatment of asthma, constipation, chronic intestinal pseudo-obstruction, and cirrhosis of the liver.

TITLE OF THE INVENTION
ACYCLIC HYDRAZIDES AS CANNABINOID RECEPTOR MODULATORS

BACKGROUND OF THE INVENTION

Marijuana (*Cannabis sativa L.*) and its derivatives have been used for centuries for medicinal and recreational purposes. A major active ingredient in marijuana and hashish has been determined to be Δ^9-tetrahydrocannabinol (Δ^9-THC). Detailed research has revealed that the biological action of Δ^9-THC and other members of the cannabinoid family occurs through two G-protein coupled receptors termed CB1 and CB2. The CB1 receptor is primarily found in the central and peripheral nervous systems and to a lesser extent in several peripheral organs. The CB2 receptor is found primarily in lymphoid tissues and cells. Three endogenous ligands for the cannabinoid receptors derived from arachidonic acid have been identified (anandamide, 2-arachidonoyl glycerol, and 2-arachidonyl glycerol ether). Each is an agonist with activities similar to Δ^9-THC, including sedation, hypothermia, intestinal immobility, antinociception, analgesia, catalepsy, anti-emesis, and appetite stimulation.

There are at least two CB1 modulators characterized as inverse agonists or antagonists, N-(1-piperidinyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide (SR141716A), and 3-(4-chlorophenyl-N'-(4-chlorophenyl)sulfonyl-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (SLV-319), in clinical trials for treatment of eating disorders and/or smoking cessation at this time. There still remains a need for potent low molecular weight CB1 modulators that have pharmacokinetic and pharmacodynamic properties suitable for use as human pharmaceuticals.

US Patents 5,624,941, 6,028,084, and 6,509,367, PCT Publications WO98/31227, WO98/41519, WO98/43636 and WO98/43635, and EP-658546 disclose substituted pyrazoles having activity against the cannabinoid receptors.

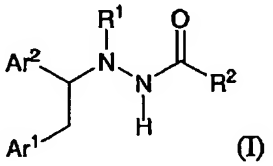
Other cannabinoid receptor modulating compounds are disclosed in US Patents 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,532,237, 6,355,631, 6,479,479 and PCT publications WO 97/29079, 98/37061, 99/02499, 00/10967, 00/10968, 01/58869, 01/64632, 01/64633, 01/64634, 01/70700, 02/076949, 03/026647, 03/026648, 03/027069, 03/027076, 03/027114, and 03/077847.

The compounds of the present invention are modulators of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the Cannabinoid-1 (CB1) receptor. Compounds of the present invention are antagonists or inverse agonists of the CB1 receptor. The invention is concerned with the use of these compounds to modulate the Cannabinoid-1 (CB1) receptor. As such, compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, such as for example, those relating to opiates, alcohol, marijuana,

and nicotine. The compounds are also useful for the treatment of eating disorders by inhibiting excessive food intake and the resulting obesity and complications associated therewith, including left ventricular hypertrophy. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction, as well as for the treatment of asthma, and cirrhosis of the liver.

SUMMARY OF THE INVENTION

The present invention is concerned with substituted aralkyl amine derivatives of general formula I:



(I)

stereoisomers and pharmaceutically acceptable salts thereof which are modulators, and in particular, antagonists and/or inverse agonists, of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention or suppression of diseases mediated by the Cannabinoid-1 (CB1) receptor. The invention is concerned with the use of these novel compounds to selectively antagonize the Cannabinoid-1 (CB1) receptor. As such, compounds of the present invention are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, such as for example, those relating to opiates, alcohol, marijuana, and nicotine, including smoking cessation. The compounds are also useful for the treatment of obesity or eating disorders associated with excessive food intake and complications associated therewith, including left ventricular hypertrophy. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction. The compounds are also useful for the treatment of cirrhosis of the liver. The compounds are also useful for the treatment of asthma.

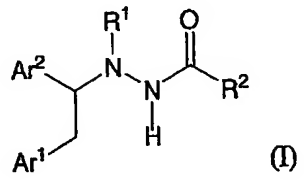
The present invention is also concerned with treatment of these conditions, and the use of compounds of the present invention for manufacture of a medicament useful in treating these conditions. The present invention is also concerned with treatment of these conditions through a combination of compounds of formula I and other currently available pharmaceuticals.

The invention is also concerned with pharmaceutical formulations comprising one of the compounds as an active ingredient.

The invention is further concerned with processes for preparing the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds used in the methods of the present invention are represented by structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 is selected from:

(1) hydrogen,
(2) C_{1-4}alkyl,
(3) C_{3-6}cycloalkyl,
(4) C_{2-4}alkenyl, and
(5) C_{2-4}alkynyl;

R^2 is selected from:

(1) C_{1-10}alkyl,
(2) C_{2-10}alkenyl,
(3) C_{2-10}alkynyl,
(4) C_{3-10}cycloalkyl,
(5) C_{3-10}cycloalkyl C_{1-4}alkyl,
(6) cycloheteroalkyl,
(7) cycloheteroalkyl C_{1-4}alkyl
(8) aryl,
(9) aryl C_{1-10}alkyl,
(10) aryl C_{2-8}alkenyl,
(11) diaryl C_{1-4}alkyl,
(12) heteroaryl,
(13) heteroaryl C_{1-10}alkyl,
(14) NR^cR^d,

wherein each alkyl, alkenyl, and alkynyl is straight or branched chain and unsubstituted or substituted with one to four substituents independently selected from R^a and each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^b;

Ar^1 and Ar^2 are independently selected from:

(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to four substituents independently selected from R^b;

each R^a is independently selected from:

(1) -OR^d,

(2) -$NR^cS(O)_mR^d$,

(3) halogen,

(4) -SR^d,

(5) –$S(O)mR^d$,

(6) -$S(O)_mNR^cR^d$,

(7) -NR^cR^d,

(8) -$C(O)R^d$,

(9) -CO_2R^d,

(10) -CN,

(11) -$C(O)NR^cR^d$,

(12) -$NR^cC(O)R^d$,

(13) -$NR^cC(O)OR^d$,

(14) -$NR^cC(O)NR^cR^d$,

(15) -CF_3, and

(16) -OCF_3;

each R^b is independently selected from:

(1) R^a,

(2) C_{1-10}alkyl,

(3) oxo,

(4) aryl,

(5) arylC_{1-4}alkyl,

(6) heteroaryl, and

(7) heteroarylC_{1-4}alkyl,

each R^c and R^d is independently selected from:

(1) hydrogen,

(2) C_{1-10}alkyl,

(3) C_{2-10} alkenyl,

(4) cycloalkyl,

(5) cycloalkyl-C_{1-10}alkyl;

(6) cycloheteroalkyl,

(7) cycloheteroalkyl-C_{1-10} alkyl,

(8) aryl,

(9) heteroaryl,

(10) pyridyl,

(11) pyrimidyl,

(12) aryl-C_{1-10}alkyl, and

(13) heteroaryl-C_{1-10}alkyl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-R^g, each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;

each R^g is independently selected from:

(1) hydrogen,

(2) C_{1-4}alkyl, and

(3) -C(O)C_{1-4}alkyl,

(4) –C(O)OR^d,

(5) –C(O)NR^cR^d,

(6) –$S(O)_mR^d$, and

(7) -$S(O)_mNR^cR^d$;

each R^h is independently selected from:

(1) halogen,

(2) C_{1-10}alkyl,

(3) -O-C_{1-4}alkyl,

(4) -S-C_{1-4}alkyl,

(5) -$S(O)_m$-C_{1-4}alkyl,

(6) -CN,

(7) -NO_2,

(8) -CF_3,

(9) -CHF_2 and

(10) -OCF_3; and

m is selected from 1 and 2.

In one embodiment of the present invention, R^1 is selected from: hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, and C_{2-4}alkynyl.

In one class of this embodiment, R^1 is selected from: hydrogen, C_{1-4}alkyl and C_{2-4}alkenyl.

In a subclass of this class, R^1 is selected from: hydrogen, methyl, ethyl, propyl, and allyl.

In another embodiment of the present invention, R^2 is selected from: C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-10}cycloalkyl, cycloheteroalkyl, aryl, aryl C_{1-10}alkyl, heteroaryl, and heteroaryl C_{1-10}alkyl, wherein:

each alkyl, alkenyl, and alkynyl is straight or branched chain and unsubstituted or substituted with one, two, three, or four substituents independently selected from R^a, and each cycloalkyl,

cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with one, two, three or four substituents independently selected from R^b.

In one class of this embodiment R^2 is selected from: C_{1-8}alkyl, C_{2-8}alkenyl, C_{3-8}cycloalkyl, cycloheteroalkyl, aryl, aryl C_{1-6}alkyl, heteroaryl, and heteroaryl C_{1-6} alkyl, wherein:

each alkyl and alkenyl is straight or branched chain and unsubstituted or substituted with one, two or three substituents independently selected from R^a, and each cycloalkyl, cycloheteroalkyl, aryl, and heteroaryl is unsubstituted or substituted with one, two or three substituents independently selected from R^b.

In one subclass of this class, R^2 is selected from:

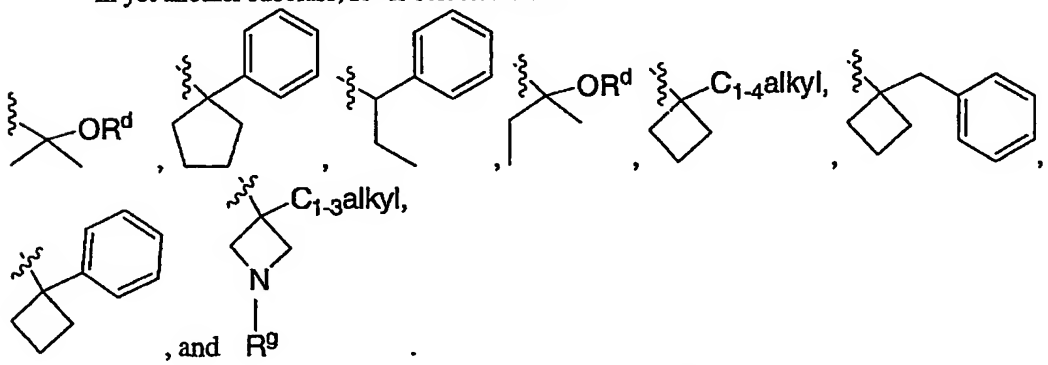
C_{1-8} alkyl, C_{3-6} cycloalkyl, cycloheteroalkyl, phenyl, phenyl C_{1-3} alkyl, pyridyl, pyrimidyl, pyridyl C_{1-3} alkyl, and pyrimidyl C_{1-3} alkyl, wherein:

each alkyl moiety is straight or branched chain and unsubstituted or substituted with one, two or three substituents independently selected from R^a, and each cycloalkyl, cycloheteroalkyl, phenyl, and heteroaryl moiety is unsubstituted or substituted with one, two or three substituents independently selected from R^b.

In another subclass, R^2 is selected from: isopropyl, n-propyl, sec-butyl, cyclopentyl, cyclobutyl, azetidinyl, 1-phenyl-propyl, wherein:

each alkyl moiety is unsubstituted or substituted with one or two R^a substituents, and each cycloalkyl, cycloheteroalkyl, or phenyl moiety is unsubstituted or substituted with one or two R^b substituents.

In yet another subclass, R^2 is selected from:



, and .

In yet another embodiment of the present invention, Ar^1 is selected from:

aryl and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one, two, three, or four substituents independently selected from R^b.

In a class of this embodiment, Ar^1 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three R^b substituents.

In a subclass of this class, Ar^1 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three substituents selected from halogen and cyano.

In another subclass of this class, Ar^1 is phenyl, unsubstituted or substituted with one or two R^b substituents.

In still another subclass, Ar^1 is phenyl unsubstituted or parasubstituted with an R^b substituent.

In yet another subclass, Ar^1 is phenyl substituted in the para-position with halogen or cyano.

In an additional subclass, Ar^1 is para-chlorophenyl.

In yet another embodiment of the present invention, Ar^2 is selected from:

aryl and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to four substituents independently selected from R^b.

In a class of this embodiment, Ar^2 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three R^b substituents.

In a subclass of this class, Ar^2 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three substituents selected from halogen and cyano.

In another subclass of this class, Ar^2 is phenyl, unsubstituted or substituted with one or two R^b substituents.

In still another subclass, Ar^2 is phenyl unsubstituted or metasubstituted with an R^b substituent.

In yet another subclass, Ar^2 is phenyl substituted in the meta-position with halogen or cyano.

In an additional subclass, Ar^2 is meta-chlorophenyl.

In an additional subclass, Ar^2 is selected from: m-chlorophenyl, m-bromophenyl, and m-cyanophenyl.

In a class of the present invention, each R^a is independently selected from: $-OR^d$, halogen, cyano, and CO_2R^d.

In a subclass of this class, each R^a is independently selected from: $-OR^d$, -Br, -Cl, -CN, and $-CO_2C(CH_3)_3$.

In an embodiment of the present invention, each R^b is independently selected from: $-OR^d$, $-NHS(O)_mR^d$, halogen, $-SR^d$, $-S(O)mR^d$, $-S(O)_mNHR^d$, $-NHR^d$, $-C(O)R^d$, $-CO_2R^d$, -CN, $-C(O)NR^cR^d$, $-NHC(O)R^d$, $-NHC(O)OR^d$, $-NHC(O)NR^cR^d$, $-CF_3$, $-OCF_3$, cycloheteroalkyl, C_{1-10}alkyl, oxo, aryl, arylC_{1-4}alkyl, heteroaryl, and heteroarylC_{1-4}alkyl.

In one class of this embodiment, each R^b is independently selected from: $-OR^d$, halogen, -CN, $-CF_3$, $-OCF_3$, cycloheteroalkyl, C_{1-4}alkyl, oxo, phenyl, benzyl, and heteroaryl.

In a subclass, each R^b is independently selected from: $-OR^d$, –F, –Cl, –Br, cyano, phenyl, benzyl, methyl, ethyl, n-propyl, isopropyl, $-CO_2H$, and $-CO_2C(CH_3)_3$.

In one embodiment of the present invention, each R^c is independently selected from:

(1) hydrogen, and

(2) C_{1-4}alkyl, and

each R^d is independently selected from:

(1) hydrogen,

(2) C_{1-4}alkyl,

(3) C_{2-6}alkenyl,
(4) cycloalkyl,
(5) cycloalkyl-C_{1-4}alkyl,
(6) cycloheteroalkyl,
(7) cycloheteroalkyl-C_{1-4} alkyl,
(8) phenyl,
(9) heteroaryl,
(10) phenyl-C_{1-4}alkyl, and
(11) heteroaryl-C_{1-4}alkyl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg, each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h.

In one class of this embodiment, each R^c is independently selected from: hydrogen, and C_{1-4}alkyl, and

each R^d is independently selected from:

(1) hydrogen,
(2) C_{1-5}alkyl,
(3) $-CH_2CH=CH_2$,
(4) cyclohexyl,
(5) cyclopentyl,
(6) cyclopropyl,
(7) cyclobutylmethyl,
(8) cyclopentylmethyl,
(9) cyclohexylmethyl,
(10) pyrrolidinyl,
(11) phenyl,
(12) thiazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) benzothiazolyl,
(16) benzoxazolyl,
(17) triazolyl,
(18) benzyl, and
(19) pyridyl-methyl-, or

R^c and R^d together with the atom(s) to which they are attached form a piperidinyl ring,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h.

In a subclass of this class, each R^c is selected from:

(1) hydrogen, and

(2) C_{1-4}alkyl, and

each R^d is independently selected from:

(1) hydrogen,

(2) phenyl,

(3) pyridyl, and

(4) pyrimidyl,

wherein phenyl, pyridyl and pyrimidyl are unsubstituted or substituted with one or two R^h substituents.

In one embodiment of the present invention, each Rg is independently selected from: hydrogen, C_{1-4}alkyl, -C(O)C_{1-4}alkyl, $-C(O)OR^d$, $-C(O)NR^cR^d$, $-S(O)_mR^d$, and $-S(O)_mNR^cR^d$.

In one class of this embodiment, each Rg is selected from: hydrogen, C_{1-4}alkyl, and -C(O)C_{1-4}alkyl.

In another class of this embodiment, each Rg is hydrogen, methyl or methylcarbonyl.

In one subclass of this class, each Rg is hydrogen or methyl.

In one embodiment of the present invention, each R^h is independently selected from: halogen, C_{1-10}alkyl, -O-C_{1-4}alkyl, -S- C_{1-4}alkyl, -S(O)$_m$-C_{1-4}alkyl, -CN, $-NO_2$, $-CF_3$, $-CHF_2$, and $-OCF_3$.

In one class of this embodiment, each R^h is independently selected from: halogen, methyl, methoxy, -CN, $-CF_3$, $-CHF_2$, and $-OCF_3$.

In another class, each R^h is independently selected from: halogen, C_{1-10}alkyl, -O-C_{1-4}alkyl, -S- C_{1-4}alkyl, -CN, $-NO_2$, $-CF_3$, $-CHF_2$, and $-OCF_3$.

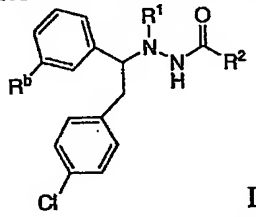
In yet another class of this embodiment, each R^h is independently selected from: halogen, methyl, methoxy, -S(O)$_m$-CH_3, -CN, $-CF_3$, $-CHF_2$, and $-OCF_3$.

In a subclass of this class, each R^h is selected from: -Cl, -F, $-CH_3$, $-CF_3$, and $-CHF_2$.

In one embodiment of the present invention m is one or two.

In a class of this embodiment, m is two. In another class, m is one.

In another embodiment of the present invention is directed to compounds of structural formula II:



II.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means mono- or bicyclic or bridged saturated carbocyclic rings, each having from 3 to 10 carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooxtyl, tetrahydronaphthyl, decahydronaphthyl, and the like.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. Examples of aryl include phenyl, naphthyl, and the like.

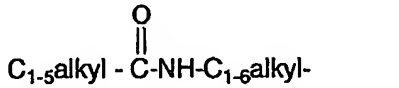
"Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzothiazolyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, oxazolidinyl, and the like. The heteroaryl ring may be substituted on one or more carbon atoms. In one embodiment of the present invention, heteroaryl is pyridyl, pyrimidyl, imidazolyl, and thienyl. In one class of this embodiment heteroaryl is pyridyl.

"Cycloheteroalkyl" means mono- or bicyclic or bridged saturated rings containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. Examples of "cycloheteroalkyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, pyranyl, tetrahydrofuranyl, morpholinyl, dioxanyl, oxanyl, azetidinyl, perhydroazepinyl, tetrahydrofuranyl, 1-thia-4-aza-cyclohexane (thiomorpholinyl), hexahydrothienopyridinyl, thienopyridinyl, azacycloheptyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted-(1H, 3H)-pyrimidine-2,4-diones (N-substituted uracils). The cycloheteroalkyl ring may be substituted on the ring carbons and/or the ring nitrogens.

"Halogen" includes fluorine, chlorine, bromine and iodine.

When any variable (e.g., R^1, R^d, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. For example, a C_{1-5} alkylcarbonylamino C_{1-6} alkyl substituent is equivalent to:



In choosing compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e., R^1, R^2, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability.

The term "substituted" shall be deemed to include multiple degrees of substitution by a named substitutent. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Tautomers are defined as compounds that undergo rapid proton shifts from one atom of the compound to another atom of the compound. Some of the compounds described herein may exist as tautomers with different points of attachment of hydrogen. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of this invention.

It is generally preferable to administer compounds of the present invention as enantiomerically pure formulations. Racemic mixtures can be separated into their individual enantiomers by any of a number of conventional methods. These include chiral chromatography, derivatization with a chiral auxiliary followed by separation by chromatography or crystallization, and fractional crystallization of diastereomeric salts.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids.

Salts derived from inorganic bases can be chosen from aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like, such as for example, ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. The term "pharmaceutically acceptable salt" further includes all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Compounds of the present invention are modulators of the CB1 receptor. In particular, the compounds of structural formula I are antagonists or inverse agonists of the CB1 receptor.

An "agonist" is a compound (hormone, neurotransmitter or synthetic compound) which binds to a receptor and mimics the effects of the endogenous regulatory compound, such as contraction, relaxation, secretion, change in enzyme activity, etc. An "antagonist" is a compound, devoid of intrinsic regulatory activity, which produces effects by interfering with the binding of the endogenous agonist or inhibiting the action of an agonist. An "inverse agonist" is a compound which acts on a receptor but produces the opposite effect produced by the agonist of the particular receptor.

Compounds of this invention are modulators of the CB1 receptor and as such are useful as centrally acting drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, such as for example, to opiates, alcohol, marijuana, and nicotine. The compounds are also useful for the treatment of obesity or eating disorders

associated with excessive food intake and complications associated therewith, including left ventricular hypertrophy. The compounds are also useful for the treatment of constipation and chronic intestinal pseudo-obstruction. The compounds are also useful for the treatment of cirrhosis of the liver. The compounds are also useful for the treatment of asthma.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The administration of the compound of structural formula I in order to practice the present methods of therapy is carried out by administering an effective amount of the compound of structural formula I to the patient in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors. The effective amount of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgment.

The utilities of the present compounds in these diseases or disorders may be demonstrated in animal disease models that have been reported in the literature. The following are examples of such animal disease models: a) suppression of food intake and resultant weight loss in rats (Life Sciences 1998, 63, 113-117); b) reduction of sweet food intake in marmosets (Behavioural Pharm. 1998, 9, 179-181); c) reduction of sucrose and ethanol intake in mice (Psychopharm. 1997, 132, 104-106); d) increased motor activity and place conditioning in rats (Psychopharm. 1998, 135, 324-332; Psychopharmacol 2000, 151: 25-30); e) spontaneous locomotor activity in mice (J. Pharm. Exp. Ther. 1996, 277, 586-594); f) reduction in opiate self-administration in mice (Sci. 1999, 283, 401-404); g) bronchial hyperresponsiveness in sheep and guinea pigs as models for the various phases of asthma (for example, see W. M. Abraham et al., "α_4-Integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep." J. Clin. Invest. 93, 776 (1993) and A. A. Y. Milne and P. P. Piper, "Role of VLA-4 integrin in leucocyte recruitment and bronchial hyperresponsiveness in the guinea-pig." Eur. J. Pharmacol., 282, 243 (1995)); h) mediation of the vasodilated state in advanced liver cirrhosis induced by carbon tetrachloride (Nature Medicine, 2001, 7 (7), 827-832); i) amitriptyline-induced constipation in cynomolgus monkeys is beneficial for the evaluation of laxatives (Biol. Pharm. Bulletin (Japan), 2000, 23(5), 657-9); j) neuropathology of paediatric chronic intestinal pseudo-obstruction and animal models related to the neuropathology of paediatric chronic intestinal pseudo-obstruction (Journal of Pathology (England), 2001, 194 (3), 277-88).

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of

the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, such as, for example, from 0.01 mg to about 50 mg per kg, and further from 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 100 mg (such as for example from 0.01 mg to about 50 mg, further from 0.1 mg to 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 1000 mg of a compound of Formula I per day, preferably from about 0.1 mg to about 10 mg per day. For oral administration, the compositions are optionally provided in the form of tablets containing from 0.01 to 1,000 mg, such as for example 0.01, 0.05, 0.1, 0.5, 1, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 100, 250, 500, 750 or 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a mammal, especially a human or companion animal such as a dog or cat, with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulizers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, solutions, ointments, gels, lotions, dusting powders, and the like. The topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.005% to 5% by weight of the active compound in admixture with a pharmaceutically acceptable vehicle. Transdermal skin patches useful for administering the compounds of the present invention include those well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course be continuous rather than intermittent throughout the dosage regimen.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules (including timed release and sustained release formulations), pills, cachets, powders, granules or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion, including elixirs, tinctures, solutions,

suspensions, syrups and emulsions. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound of the invention moistened with an inert liquid diluent. Desirably, each tablet cachet or capsule contains from about 0.01 to 1,000 mg, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 3, 5, 6, 10, 15, 25, 30, 40, 50, 75, 100, 125, 150, 175, 180, 200, 225, 250, 500, 750 and 1,000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated.

Additional suitable means of administration of the compounds of the present invention include injection, intravenous bolus or infusion, intraperitoneal, subcutaneous, intramuscular and topical, with or without occlusion.

Exemplifying the invention is a pharmaceutical composition comprising any of the compounds described above and a pharmaceutically acceptable carrier. Also exemplifying the invention is a pharmaceutical composition made by combining any of the compounds described above and a pharmaceutically acceptable carrier. An illustration of the invention is a process for making a pharmaceutical composition comprising combining any of the compounds described above and a pharmaceutically acceptable carrier.

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, based on the properties of the individual compound selected for administration, the dose may be administered less frequently, e.g., weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

When administered via intranasal routes, transdermal routes, by rectal or vaginal suppositories, or through a continual intravenous solution, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The following are examples of representative pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL	Tablet	mg/tablet
Compound of Formula I	10	Compound of Formula I	25
Methylcellulose	5.0	Microcrystalline Cellulose	415
Tween 80	0.5	Povidone	14.0

Benzyl alcohol	9.0	Pregelatinized Starch	43.5
Benzalkonium chloride	1.0	Magnesium Stearate	2.5
Water for injection to a total volume of 1 mL			500

Capsule	mg/capsule	Aerosol	Per canister
Compound of Formula I	25	Compound of Formula I	24 mg
Lactose Powder	573.5	Lecithin, NF Liq. Conc.	1.2 mg
Magnesium Stearate	1.5	Trichlorofluoromethane, NF	4.025 g
	600	Dichlorodifluoromethane, NF	12.15 g

Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I include, but are not limited to: antipsychotic agents, cognition enhancing agents, anti-migraine agents, anti-asthmatic agents, antiinflammatory agents, anxiolytics, anti-Parkinson's agents, anti-epileptics, anorectic agents, serotonin reuptake inhibitors, other anti-obesity agents, as well as antidiabetic agents, lipid lowering agents, and antihypertensive agents which may be administered separately or in the same pharmaceutical compositions.

The present invention also provides a method for the treatment or prevention of a CB1 receptor modulator mediated disease, which method comprises administration to a patient in need of such treatment or at risk of developing a CB1 receptor modulator mediated disease of an amount of a CB1 receptor modulator and an amount of one or more active ingredients, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CB1 receptor modulator and one or more active ingredients, together with at least one pharmaceutically acceptable carrier or excipient.

Thus, according to a further aspect of the present invention there is provided the use of a CB1 receptor modulator and one or more active ingredients for the manufacture of a medicament for the treatment or prevention of a CB1 receptor modulator mediated disease. In a further or alternative aspect of the present invention, there is therefore provided a product comprising a CB1 receptor modulator and one or more active ingredients as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of CB1 receptor modulator mediated disease. Such a combined preparation may be, for example, in the form of a twin pack.

It will be appreciated that for the treatment or prevention of eating disorders, including obesity, bulimia nervosa and compulsive eating disorders, a compound of the present invention may be used in conjunction with other anorectic agents.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anorectic agent, such that together they give effective relief.

Suitable anorectic agents of use in combination with a compound of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, *N*-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

One non-limiting class of anorectic agents includes the halogenated amphetamine derivatives, such as for example, chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof

One embodiment includes the combination of a compound in accordance with the invention admixed with halogenated amphetamine derivatives selected from fenfluramine, dexfenfluramine, and pharmaceutically acceptable salts thereof.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of another agent useful in treating obesity and obesity-related conditions, such that together they give effective relief.

Suitable anti-obesity agents of use in combination with a compound of the present invention, include, but are not limited to:

(a) anti-diabetic agents such as (1) PPARγ agonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone (ACTOS); rosiglitazone (AVANDIA); troglitazone; rivoglitazone, BRL49653; CLX-0921; 5-BTZD, GW-0207, LG-100641, R483, and LY-300512, and the like and compounds disclosed in WO97/10813, 97/27857, 97/28115, 97/28137, 97/27847, 03/000685, and 03/027112 and SPPARMS (selective PPAR gamma modulators) such as T131 (Amgen), FK614 (Fujisawa), netoglitazone, and metaglidasen; (2) biguanides such as buformin; metformin; and phenformin, and the like; (3) protein tyrosine phosphatase-1B (PTP-1B) inhibitors such as ISIS 113715, A-401674, A-364504, IDD-3, IDD 2846, KP-40046, KR61639, MC52445, MC52453, C7, OC-060062, OC-86839, OC29796, TTP-277BC1, and those agents disclosed in WO 04/041799, 04/050646, 02/26707, 02/26743, 04/092146, 03/048140, 04/089918, 03/002569, 04/065387, 04/127570, and US 2004/167183; (4) sulfonylureas such as acetohexamide; chlorpropamide; diabinese;

glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide, and the like; (5) meglitinides such as repaglinide, metiglinide (GLUFAST) and nateglinide, and the like; (6) alpha glucoside hydrolase inhibitors such as acarbose; adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (7) alpha-amylase inhibitors such as tendamistat, trestatin, and Al-3688, and the like; (8) insulin secreatagogues such as linogliride nateglinide, mitiglinide (GLUFAST), ID1101 A-4166, and the like; (9) fatty acid oxidation inhibitors, such as clomoxir, and etomoxir, and the like; (10) A2 antagonists, such as midaglizole; isaglidole; deriglidole; idazoxan; earoxan; and fluparoxan, and the like; (11) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (17-36), GLP-1 (73-7) (insulintropin); GLP-1 (7-36)-NH_2) exenatide/Exendin-4, Exenatide LAR, Linaglutide, AVE0010, CJC 1131, BIM51077, CS 872, THO318, BAY-694326, GP010, ALBUGON (GLP-1 fused to albumin), HGX-007 (Epac agonist), S-23521, and compounds disclosed in WO 04/022004, WO 04/37859, and the like; (12) non-thiazolidinediones such as JT-501, and farglitazar (GW-2570/GI-262579), and the like; (13) PPARα/γ dual agonists such as AVE 0847, CLX-0940, GW-1536, GW1929, GW-2433, KRP-297, L-796449, LBM 642, LR-90, LY510919, MK-0767, ONO 5129, SB 219994, TAK-559, TAK-654, 677954 (GlaxoSmithkline), E-3030 (Eisai), LY510929 (Lilly), AK109 (Asahi), DRF2655 (Dr. Reddy), DRF8351 (Dr. Reddy), MC3002 (Maxocore), TY51501 (ToaEiyo), naveglitazar, muraglitizar, peliglitazar, tesaglitazar (GALIDA), reglitazar (JTT-501), chiglitazar, and those disclosed in WO 99/16758, WO 99/19313, WO 99/20614, WO 99/38850, WO 00/23415, WO 00/23417, WO 00/23445, WO 00/50414, WO 01/00579, WO 01/79150, WO 02/062799, WO 03/033481, WO 03/033450, WO 03/033453; and (14) other insulin sensitizing drugs; (15) VPAC2 receptor agonists; (16) GLK modulators, such as PSN105, RO 281675, RO 274375 and those disclosed in WO 03/015774, WO 03/000262, WO 03/055482, WO 04/046139, WO 04/045614, WO 04/063179, WO 04/063194, WO 04/050645, and the like; (17) retinoid modulators such as those disclosed in WO 03/000249; (18) GSK 3beta/GSK 3 inhibitors such as 4-[2-(2-bromophenyl)-4-(4-fluorophenyl-1H-imidazol-5-yl]pyridine, CT21022, CT20026, CT-98023, SB-216763, SB410111, SB-675236, CP-70949, XD4241 and those compounds disclosed in WO 03/037869, 03/03877, 03/037891, 03/024447, 05/000192, 05/019218 and the like; (19) glycogen phosphorylase (HGLPa) inhibitors, such as AVE 5688, PSN 357, GPi-879, those disclosed in WO 03/037864, WO 03/091213, WO 04/092158, WO 05/013975, WO 05/013981, US 2004/0220229, and JP 2004-196702, and the like; (20) ATP consumption promotors such as those disclosed in WO 03/007990; (21) fixed combinations of PPAR γ agonists and metformin such as AVANDAMET; (22) PPAR pan agonists such as GSK 677954; (23) GPR40 (G-protein coupled receptor 40) also called SNORF 55 such as BG 700, and those disclosed in WO 04/041266, 04/022551, 03/099793; (24) GPR119 (also called RUP3; SNORF 25) such as RUP3, HGPRBMY26, PFI 007, SNORF 25; (25) adenosine receptor 2B antagonists such as ATL-618, ATl-802, E3080, and the like; (26) carnitine palmitoyl transferase inhibitors such as ST 1327, and ST 1326, and the like; (27) Fructose 1,6-

bisphospohatase inhibitors such as CS-917, MB7803, and the like; (28) glucagon antagonists such as AT77077, BAY 694326, GW 4123X, NN2501, and those disclosed in WO 03/064404, WO 05/00781, US 2004/0209928, US 2004/029943, and the like; (30) glucose-6-phosphase inhibitors; (31) phosphoenolpyruvate carboxykinase (PEPCK) inhibitors; (32) pyruvate dehydrogenase kinase (PDK) activators; (33) RXR agonists such as MC1036, CS00018, JNJ 10166806, and those disclosed in WO 04/089916, US 6759546, and the like; (34) SGLT inhibitors such as AVE 2268, KGT 1251, T1095/RWJ 394718; (35) BLX-1002;

(b) lipid lowering agents such as (1) bile acid sequestrants such as, cholestyramine, colesevelem, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®; and Questran®, and the like; (2) HMG-CoA reductase inhibitors such as atorvastatin, itavastatin, pitavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, rosuvastatin (ZD-4522), and the like, particularly simvastatin; (3) HMG-CoA synthase inhibitors; (4) cholesterol absorption inhibitors such as FMVP4 (Forbes Medi-Tech), KT6-971 (Kotobuki Pharmaceutical), FM-VA12 (Forbes Medi-Tech), FM-VP-24 (Forbes Medi-Tech), stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and those disclosed in WO 04/005247and the like; (5) acyl coenzyme A -cholesterol acyl transferase (ACAT) inhibitors such as avasimibe, eflucimibe, pactimibe (KY505), SMP 797 (Sumitomo), SM32504 (Sumitomo), and those disclosed in WO 03/091216, and the like; (6) CETP inhibitors such as JTT 705 (Japan Tobacco), torcetrapib, CP 532,632, BAY63-2149 (Bayer), SC 591, SC 795, and the like; (7) squalene synthetase inhibitors; (8) anti-oxidants such as probucol, and the like; (9) PPARα agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, gemcabene, and gemfibrozil, GW 7647, BM 170744 (Kowa), LY518674 (Lilly), GW590735 (GlaxoSmithkline), KRP-101 (Kyorin), DRF10945 (Dr. Reddy), NS-220/R1593 (Nippon Shinyaku/Roche, ST1929 (Sigma Tau) MC3001/MC3004 (MaxoCore Pharmaceuticals, gemcabene calcium, other fibric acid derivatives, such as Atromid®, Lopid® and Tricor®, and those disclosed in US 6,548,538, and the like; (10) FXR receptor modulators such as GW 4064 (GlaxoSmithkline), SR 103912, QRX401, LN-6691 (Lion Bioscience), and those disclosed in WO 02/064125, WO 04/045511, and the like; (11) LXR receptor modulators such as GW 3965 (GlaxoSmithkline), T9013137, and XTCO179628 (X-Ceptor Therapeutics/Sanyo), and those disclosed in WO 03/031408, WO 03/063796, WO 04/072041, and the like; (12) lipoprotein synthesis inhibitors such as niacin; (13) renin angiotensin system inhibitors; (14) PPAR δ partial agonists, such as those disclosed in WO 03/024395; (15) bile acid reabsorption inhibitors, such as BARI 1453, SC435, PHA384640, S8921, AZD7706, and the like; and bile acid sequesterants such as colesevelam (WELCHOL/CHOLESTAGEL), (16) PPARδ agonists such as GW 501516 (Ligand, GSK), GW 590735, GW-0742 (GlaxoSmithkline), T659 (Amgen/Tularik), LY934 (Lilly), NNC610050 (Novo Nordisk) and those disclosed in WO97/28149, WO 01/79197, WO 02/14291, WO 02/46154, WO 02/46176, WO 02/076957, WO 03/016291, WO 03/033493, WO 03/035603, WO 03/072100, WO 03/097607, WO 04/005253, WO 04/007439, and JP10237049, and the like; (17) triglyceride synthesis inhibitors; (18)

microsomal triglyceride transport (MTTP) inhibitors, such as implitapide, LAB687, JTT130 (Japan Tobacco), CP346086, and those disclosed in WO 03/072532, and the like; (19) transcription modulators; (20) squalene epoxidase inhibitors; (21) low density lipoprotein (LDL) receptor inducers; (22) platelet aggregation inhibitors; (23) 5-LO or FLAP inhibitors; and (24) niacin receptor agonists including HM74A receptor agonists; (25) PPAR modulators such as those disclosed in WO 01/25181, WO 01/79150, WO 02/79162, WO 02/081428, WO 03/016265, WO 03/033453; (26) niacin-bound chromium, as disclosed in WO 03/039535; (27) substituted acid derivatives disclosed in WO 03/040114; (28) infused HDL such as LUV/ETC-588 (Pfizer), APO-A1 Milano/ETC216 (Pfizer), ETC-642 (Pfizer), ISIS301012, D4F (Bruin Pharma), synthetic trimeric ApoA1, Bioral Apo A1 targeted to foam cells, and the like; (29) IBAT inhibitors such as BARI143/HMR145A/ HMR1453 (Sanofi-Aventis, PHA384640E (Pfizer), S8921 (Shionogi) AZD7806 (AstrZeneca), AK105 (Asah Kasei), and the like; (30) Lp-PLA2 inhibitors such as SB480848 (GlaxoSmithkline), 659032 (GlaxoSmithkline), 677116 (GlaxoSmithkline), and the like; (31) other agents which affect lipic composition including ETC1001/ESP31015 (Pfizer), ESP-55016 (Pfizer), AGI1067 (AtheroGenics), AC3056 (Amylin), AZD4619 (AstrZeneca); and

(c) anti-hypertensive agents such as (1) diuretics, such as thiazides, including chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, and hydrochlorothiazide; loop diuretics, such as bumetanide, ethacrynic acid, furosemide, and torsemide; potassium sparing agents, such as amiloride, and triamterene; and aldosterone antagonists, such as spironolactone, epirenone, and the like; (2) beta-adrenergic blockers such as acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol, and the like; (3) calcium channel blockers such as amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil, and the like; (4) angiotensin converting enzyme (ACE) inhibitors such as benazepril; captopril; cilazapril; delapril; enalapril; fosinopril; imidapril; losinopril; moexipril; quinapril; quinaprilat; ramipril; perindopril; perindropril; quanipril; spirapril; tenocapril; trandolapril, and zofenopril, and the like; (5) neutral endopeptidase inhibitors such as omapatrilat, cadoxatril and ecadotril, fosidotril, sampatrilat, AVE7688, ER4030, and the like; (6) endothelin antagonists such as tezosentan, A308165, and YM62899, and the like; (7) vasodilators such as hydralazine, clonidine, minoxidil, and nicotinyl alcohol, and the like; (8) angiotensin II receptor antagonists such as candesartan, eprosartan, irbesartan, losartan, pratosartan, tasosartan, telmisartan, valsartan, and EXP-3137, FI6828K, and RNH6270, and the like; (9) α/βadrenergic blockers as nipradilol, arotinolol and amosulalol, and the like; (10) alpha 1 blockers, such as terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHIP 164, and XEN010, and the like; (11) alpha 2 agonists such as lofexidine, tiamenidine, moxonidine, rilmenidine and guanobenz, and the like; and (12) aldosterone inhibitors, and the like; and

(d) anti-obesity agents, such as (1) 5HT (serotonin) transporter inhibitors, such as paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, and imipramine, and those disclosed in WO 03/00663, as well as serotonin/noradrenaline re uptake inhibitors such as sibutramine (MERIDIA/REDUCTIL) and dopamine uptake inhibitor/Norepenephrine uptake inhibitors such as radafaxine hydrochloride, 353162 (GlaxoSmithkline), and the like; (2) NE (norepinephrine) transporter inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (3) CB1 (cannabinoid-1 receptor) antagonist/inverse agonists, such as rimonabant (ACCOMPLIA Sanofi Synthelabo), SR-147778 (Sanofi Synthelabo), AVE1625 (Sanofi-Aventis), BAY 65-2520 (Bayer), SLV 319 (Solvay), SLV326 (Solvay), CP945598 (Pfizer), E-6776 (Esteve), O1691 (Organix), ORG14481 (Organon), VER24343 (Vernalis), NESS0327 (Univ of Sassari/Univ of Cagliari), and those disclosed in US Patent Nos. 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,532,237, 5,624,941, 6,028,084, and 6,509367; and WO 96/33159, WO97/29079, WO98/31227, WO 98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO 01/09120, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, WO 01/70700, WO 01/96330, WO 02/076949, WO 03/006007, WO 03/007887, WO 03/020217, WO 03/026647, WO 03/026648, WO 03/027069, WO 03/027076, WO 03/027114, WO 03/037332, WO 03/040107, WO 04/096763, WO 04/111039, WO 04/111033, WO 04/111034, WO 04/111038, WO 04/013120, WO 05/000301, WO 05/016286, WO 05/066126 and EP-658546 and the like; (4) ghrelin agonists/antagonists, such as BVT81-97 (BioVitrum), RC1291 (Rejuvenon), SRD-04677 (Sumitomo), unacylated ghrelin (TheraTechnologies), and those disclosed in WO 01/87335, WO 02/08250, WO 05/012331, and the like; (5) H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, and those disclosed in WO 02/15905; and O-[3-(1H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO 03/024928 and WO 03/024929; (6) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), T71 (Takeda/Amgen), AMGN-608450, AMGN-503796 (Amgen), 856464 (GlaxoSmithkline), A224940 (Abbott), A798 (Abbott), ATC0175/AR224349 (Arena Pharmaceuticals), GW803430 (GlaxoSmithkine), NBI-1A (Neurocrine Biosciences), NGX-1 (Neurogen), SNP-7941 (Synaptic), SNAP9847 (Synaptic), T-226293 (Schering Plough), TPI-1361-17 (Saitama Medical School/University of California Irvine), and those disclosed WO 01/21169, WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027, WO 03/13574, WO 03/15769, WO 03/028641, WO 03/035624, WO 03/033476, WO 03/033480, WO 04/004611, WO 04/004726, WO 04/011438, WO 04/028459, WO

04/034702, WO 04/039764, WO 04/052848, WO 04/087680; and Japanese Patent Application Nos. JP 13226269, JP 1437059, JP2004315511, and the like; (7) MCH2R (melanin concentrating hormone 2R) agonist/antagonists; (8) NPY1 (neuropeptide Y Y1) antagonists, such as BMS205749, BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A; and those disclosed in U.S. Patent No. 6,001,836; and WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (9) NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, S2367 (Shionogi), E-6999 (Esteve), GW-569180A, GW-594884A (GlaxoSmithkline), GW-587081X, GW-548118X; FR 235,208; FR226928, FR 240662, FR252384; 1229U91, GI-264879A, CGP71683A, C-75 (Fasgen) LY-377897, LY366377, PD-160170, SR-120562A, SR-120819A,S2367 (Shionogi), JCF-104, and H409/22; and those compounds disclosed in U.S. Patent Nos. 6,140,354, 6,191,160, 6,258,837, 6,313,298, 6,326,375, 6,329,395, 6,335,345, 6,337,332, 6,329,395, and 6,340,683 ; and EP-01010691, EP-01044970, and FR252384; and PCT Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/27063, WO 00/107409, WO 00/185714, WO 00/185730, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/20488, WO 02/22592, WO 02/48152, WO 02/49648, WO 02/051806, WO 02/094789, WO 03/009845, WO 03/014083, WO 03/022849, WO 03/028726, WO 05/014592, WO 05/01493; and Norman et al., J. Med. Chem. 43:4288-4312 (2000); (10) leptin, such as recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (11) leptin derivatives, such as those disclosed in Patent Nos. 5,552,524; 5,552,523; 5,552,522; 5,521,283; and WO 96/23513; WO 96/23514; WO 96/23515; WO 96/23516; WO 96/23517; WO 96/23518; WO 96/23519; and WO 96/23520; (12) opioid antagonists, such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, and naltrexone; and those disclosed in WO 00/21509; (13) orexin antagonists, such as SB-334867-A (GlaxoSmithkline); and those disclosed in WO 01/96302, 01/68609, 02/44172, 02/51232, 02/51838, 02/089800, 02/090355, 03/023561, 03/032991, 03/037847, 04/004733, 04/026866, 04/041791, 04/085403, and the like; (14) BRS3 (bombesin receptor subtype 3) agonists; (15) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623, PD170292, PD 149164, SR146131, SR125180, butabindide, and those disclosed in US 5,739,106; (16) CNTF (ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline); SR146131 (Sanofi Synthelabo); butabindide; and PD170,292, PD 149164 (Pfizer); (17) CNTF derivatives, such as axokine (Regeneron); and those disclosed in WO 94/09134, WO 98/22128, and WO 99/43813; (18) GHS (growth hormone secretagogue receptor) agonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429 and L-163,255, and those disclosed in U.S. Patent No. 6358951, U.S. Patent Application Nos. 2002/049196 and 2002/022637; and WO 01/56592, and WO 02/32888; (19) 5HT2c (serotonin receptor 2c) agonists, such as APD3546/AR10A (Arena Pharmaceuticals), ATH88651 (Athersys), ATH88740 (Athersys), BVT933 (Biovitrum/GSK), DPCA37215 (BMS), IK264; LY448100 (Lilly), PNU 22394; WAY 470 (Wyeth), WAY629 (Wyeth), WAY161503 (Biovitrum), R-1065, VR1065

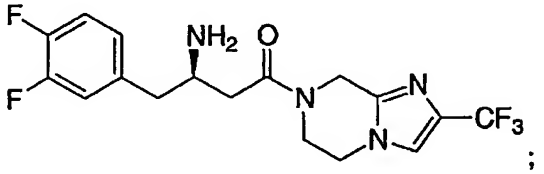
(Vernalis/Roche) YM 348; and those disclosed in U.S. Patent No. 3,914,250; and PCT Publications 01/66548, 02/36596, 02/48124, 02/10169, 02/44152; 02/51844, 02/40456, 02/40457, 03/057698, 05/000849, and the like; (20) Mc3r (melanocortin 3 receptor) agonists; (21) Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), CHIR915 (Chiron); ME-10142 (Melacure), ME-10145 (Melacure), HS-131 (Melacure), NBI72432 (Neurocrine Biosciences), NNC 70-619 (Novo Nordisk), TTP2435 (Transtech)and those disclosed in PCT Publications WO 99/64002, 00/74679, 01/991752, 01/0125192, 01/52880, 01/74844, 01/70708, 01/70337, 01/91752, 01/010842, 02/059095, 02/059107, 02/059108, 02/059117, 02/062766, 02/069095, 02/12166, 02/11715, 02/12178, 02/15909, 02/38544, 02/068387, 02/068388, 02/067869, 02/081430, 03/06604, 03/007949, 03/009847, 03/009850, 03/013509, 03/031410, 03/094918, 04/028453, 04/048345, 04/050610, 04/075823, 04/083208, 04/089951, 05/000339, and EP 1460069, and US 2005049269, and JP2005042839, and the like; (22) monoamine reuptake inhibitors, such as sibutratmine (Meridia ®/Reductil®) and salts thereof, and those compounds disclosed in U.S. Patent Nos. 4,746,680, 4,806,570, and 5,436,272, and U.S. Patent Publication No. 2002/0006964, and WO 01/27068, and WO 01/62341; (23) serotonin reuptake inhibitors, such as dexfenfluramine, fluoxetine, and those in U.S. Patent No. 6,365,633, and WO 01/27060, and WO 01/162341; (24) GLP-1 (glucagon-like peptide 1) agonists; (25) Topiramate (Topimax®); (26) phytopharm compound 57 (CP 644,673); (27) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (28) β3 (beta adrenergic receptor 3) agonists, such as rafebergron/AD9677/TAK677 (Dainippon/ Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GRC1087 (Glenmark Pharmaceuticals) GW 427353 (solabegron hydrochloride), Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), KT07924 (Kissei), SR 59119A, and those disclosed in US Patent Nos. 5,705,515, US 5,451,677; and WO94/18161, WO95/29159, WO97/46556, WO98/04526 WO98/32753, WO 01/74782, WO 02/32897, WO 03/014113, WO 03/016276, WO 03/016307, WO 03/024948, WO 03/024953, WO 03/037881, WO 04/108674, and the like; (29) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (30) DGAT2 (diacylglycerol acyltransferase 2)inhibitors; (31) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (32) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast, as well as those described in WO 03/037432, WO 03/037899; (33) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO 02/15845; and Japanese Patent Application No. JP 2000256190; (34) UCP-1 (uncoupling protein 1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), and retinoic acid; and those disclosed in WO 99/00123; (35) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (36) glucocorticoid receptor antagonists, such as CP472555 (Pfizer), KB 3305, and those disclosed in WO 04/000869, WO 04/075864, and the like; (37) 11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498 (AMG 331), BVT 2733, 3-(1-adamantyl)-4-ethyl-5-(ethylthio)-4H-1,2,4-triazole, 3-(1-adamantyl)-5-(3,4,5-trimethoxyphenyl)-4-methyl-4H-1,2,4-triazole, 3-adamantanyl-

4,5,6,7,8,9,10,11,12,3a-decahydro-1,2,4-triazolo[4,3-a][11]annulene, and those compounds disclosed in WO 01/90091, 01/90090, 01/90092, 02/072084, 04/011410, 04/033427, 04/041264, 04/027047, 04/056744, 04/065351, 04/089415, 04/037251, and the like; (38) SCD-1 (stearoyl-CoA desaturase-1) inhibitors; (39) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, saxagliptin, NVP-DPP728, LAF237 (vildagliptin), P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, GSK 823093, E 3024, SYR 322, TS021, SSR 162369, GRC 8200, K579, NN7201, CR 14023, PHX 1004, PHX 1149, PT-630, SK-0403; and the compounds disclosed in WO 02/083128, WO 02/062764, WO 02/14271, WO 03/000180, WO 03/000181, WO 03/000250, WO 03/002530, WO 03/002531, WO 03/002553, WO 03/002593, WO 03/004498, WO 03/004496, WO 03/005766, WO 03/017936, WO 03/024942, WO 03/024965, WO 03/033524, WO 03/055881, WO 03/057144, WO 03/037327, WO 04/041795, WO 04/071454, WO 04/0214870, WO 04/041273, WO 04/041820, WO 04/050658, WO 04/046106, WO 04/067509, WO 04/048532, WO 04/099185, WO 04/108730, WO 05/009956, WO 04/09806, WO 05/023762, US 2005/043292, and EP 1 258 476; (40) lipase inhibitors, such as tetrahydrolipstatin (orlistat/XENICAL), ATL962 (Alizyme/Takeda), GT389255 (Genzyme/Peptimmune)Triton WR1339, RHC80267, lipstatin, teasaponin, and diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in WO 01/77094, WO 04/111004, and U.S. Patent Nos. 4,598,089, 4,452,813, 5,512,565, 5,391,571, 5,602,151, 4,405,644, 4,189,438, and 4,242,453, and the like; (41) fatty acid transporter inhibitors; (42) dicarboxylate transporter inhibitors; (43) glucose transporter inhibitors; and (44) phosphate transporter inhibitors; (45) anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO 00/18749, WO 01/32638, WO 01/62746, WO 01/62747, and WO 03/015769; (46) peptide YY and PYY agonists such as PYY336 (Nastech/Merck), AC162352 (IC Innovations/Curis/Amylin), TM30335/TM30338 (7TM Pharma), PYY336 (Emisphere Tehcnologies), pegylated peptide YY3-36, those disclosed in WO 03/026591, 04/089279, and the like; (47) lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO 03/011267; (48) transcription factor modulators such as those disclosed in WO 03/026576; (49) Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO 97/19952, WO 00/15826, WO 00/15790, US 20030092041, and the like; (50) Brain derived neutotropic factor (BDNF), (51) Mc1r (melanocortin 1 receptor modulators such as LK-184 (Proctor & Gamble), and the like; (52) 5HT6 antagonists such as BVT74316 (BioVitrum), BVT5182c (BioVitrum), E-6795 (Esteve), E-6814 (Esteve), SB399885 (GlaxoSmithkline), SB271046 (GlaxoSmithkline), RO-046790 (Roche), and the like; (53) fatty acid transport protein 4 (FATP4); (54) acetyl-CoA carboxylase (ACC) inhibitors such as CP640186, CP610431, CP640188 (Pfizer); (55) C-terminal growth hormone fragments such as AOD9604 (Monash Univ/Metabolic Pharmaceuticals), and the like; (56) oxyntomodulin; (57) neuropeptide FF receptor antagonists such as those disclosed in WO 04/083218, and the like; (58) amylin agonists such as Symlin/pramlintide/AC137 (Amylin); (59) Hoodia and trichocaulon extracts; (60)

BVT74713 and other gut lipid appetite suppressants; (61) dopamine agonists such as bupropion (WELLBUTRIN/GlaxoSmithkline); (62) zonisamide (ZONEGRAN/Dainippon/Elan), and the like.

Specific NPY5 antagonists of use in combination with a compound of the present invention are selected from the group consisting of: 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide,3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, trans-3'-oxo-N-(5-phenyl-2-pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3'-oxo-N-[1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran- 1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, and pharmaceutically acceptable salts and esters thereof.

Specific DP-IV inhibitors of use in combination with a compound of the present invention are selected from: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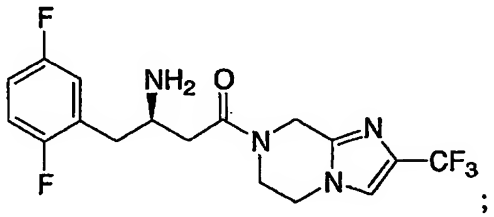
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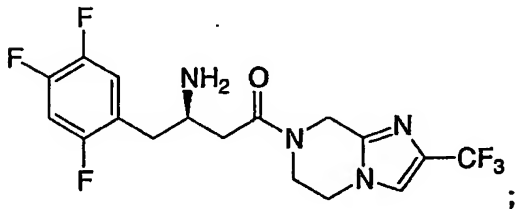
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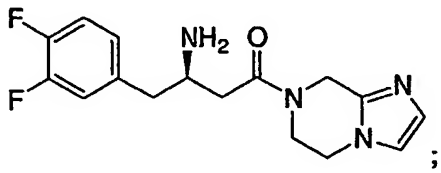
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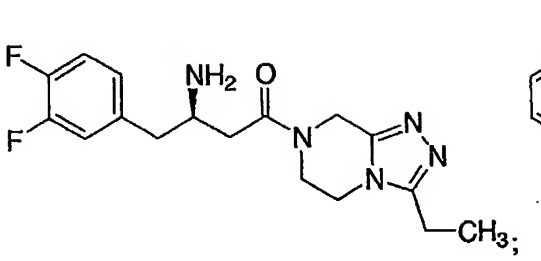
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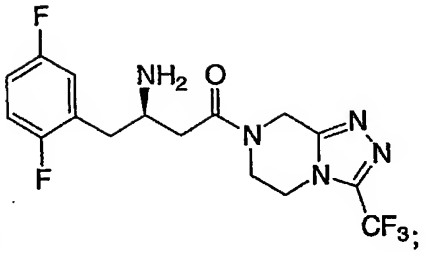
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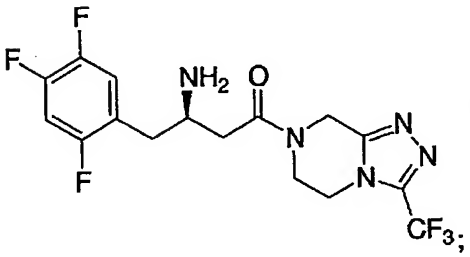
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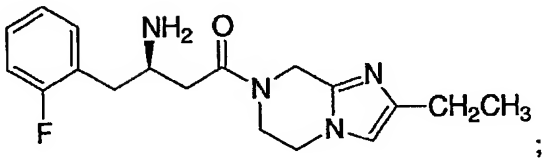
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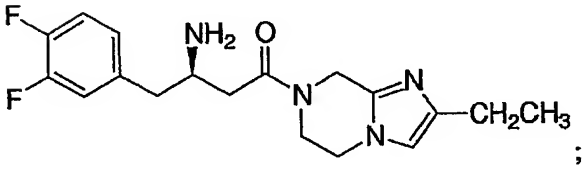
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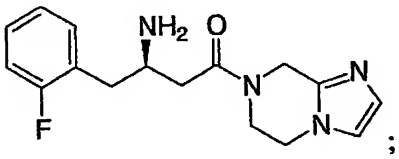
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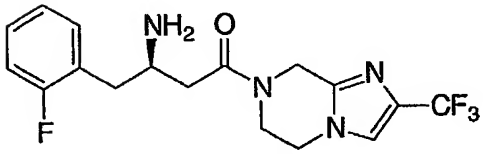
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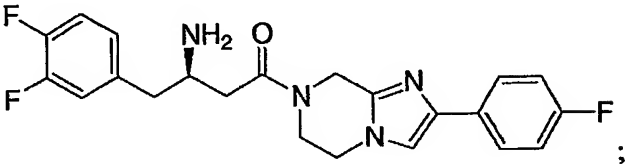
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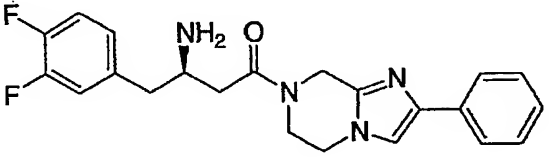
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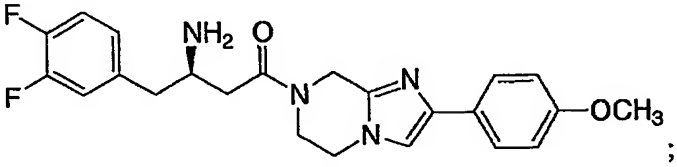
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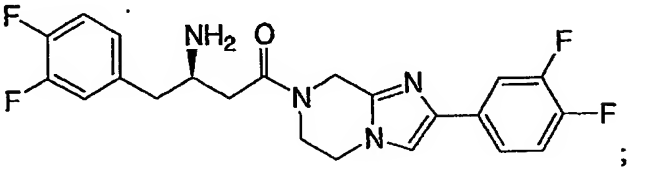
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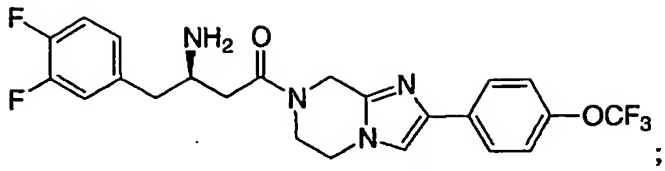
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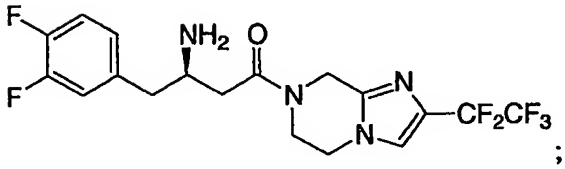
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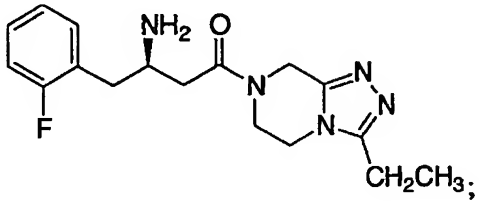
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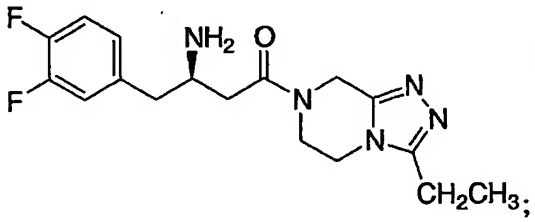
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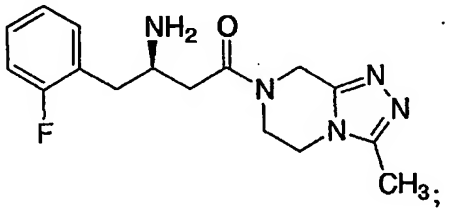
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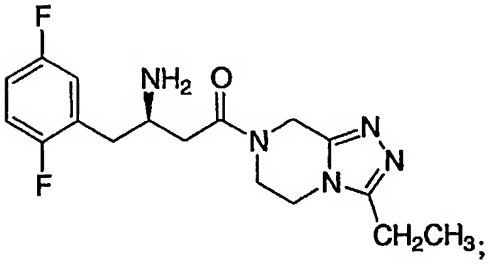
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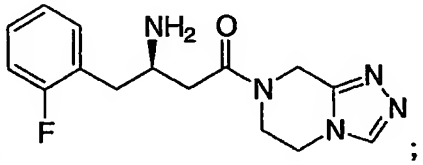
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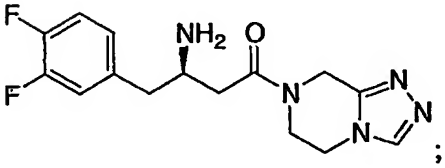
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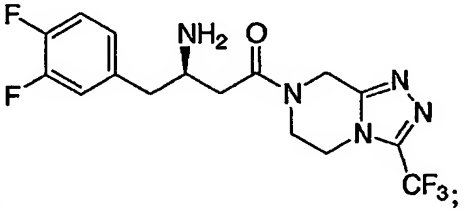
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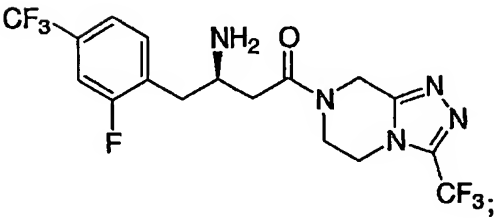
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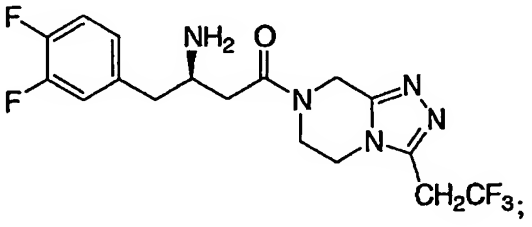
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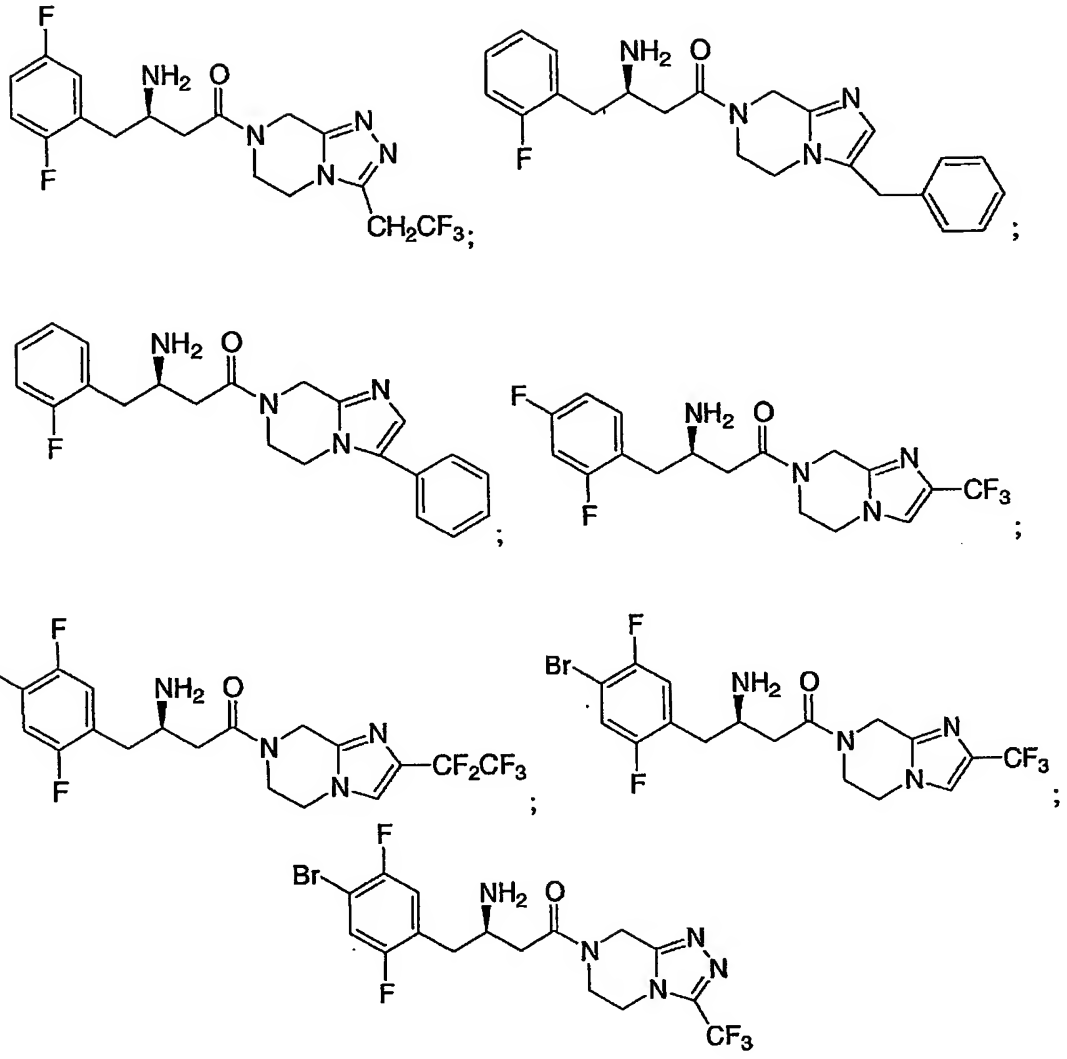

and pharmaceutically acceptable salts thereof. In particular, the compound of formula I is favorably combined with 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine.

"Obesity" is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). "Obesity" refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m^2, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m^2. An "obese subject" is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2. A "subject at risk for obesity" is an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2 or a subject with at least one co-morbidity with a BMI of 25 kg/m^2 to less than 27 kg/m^2.

The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, "obesity" refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m^2. In Asian countries, including Japan, an "obese subject" refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with a BMI greater than or equal to 25 kg/m^2. In Asian countries, a "subject at risk of obesity" is a subject with a BMI of greater than 23 kg/m^2 to less than 25 kg/m^2.

As used herein, the term "obesity" is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes, non-insulin dependent diabetes mellitus - type 2, impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, fatty liver, cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. A subset of the co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, diabetes mellitus, and other obesity-related conditions.

"Treatment" (of obesity and obesity-related disorders) refers to the administration of the compounds of the present invention to reduce or maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

"Prevention" (of obesity and obesity-related disorders) refers to the administration of the compounds of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a

subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

The obesity-related disorders herein are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer. The compounds of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

The term "diabetes," as used herein, includes both insulin-dependent diabetes mellitus (i.e., IDDM, also known as type I diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also known as Type II diabetes. Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese. The compounds of the present invention are useful for treating both Type I and Type II diabetes. The compounds are especially effective for treating Type II diabetes. The compounds of the present invention are also useful for treating and/or preventing gestational diabetes mellitus.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT_1 agonists, especially sumatriptan, naratriptan, zolmatriptan or rizatriptan.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents.

Suitable classes of anti-depressant agents include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, neurokinin-1 receptor antagonists and atypical anti-depressants.

Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof. Suitable selective serotonin reuptake inhibitors include: fluoxetine, fluvoxamine, paroxetine, imipramine and sertraline, and pharmaceutically acceptable salts thereof. Suitable monoamine oxidase inhibitors include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof. Suitable reversible inhibitors of monoamine oxidase include: moclobemide, and pharmaceutically acceptable salts thereof. Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.

Suitable CRF antagonists include those compounds described in International Patent Specification Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677.

Still further, neurokinin-1 (NK-1) receptor antagonistsmay be favorably employed with the CB1 receptor modulators of he present invention. NK-1 receptor antagonists of use in the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129,

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Specific NK-1 antagonists of use in the present invention include: (±)-(2R3R,2S3S)-N-{[2-cyclopropoxy-5-(trifluoromethoxy)-phenyl]methyl}-2-phenylpiperidin-3-amine; 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine; operpitant; CJ17493; GW597599; GW679769; R673; R067319; R1124; R1204; SSR246977; SSR2400600; T2328; and T2763; or a pharmaceutically acceptable salt thereof.

Suitable atypical anti-depressants include: bupropion, lithium, nefazodone, trazodone and viloxazine, and pharmaceutically acceptable salts thereof.

Suitable classes of anti-anxiety agents include benzodiazepines and 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists.

Suitable benzodiazepines include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.

Suitable 5-HT_{1A} receptor agonists or antagonists include, for example, the 5-HT_{1A} receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

Suitable corticotropin releasing factor (CRF) antagonists include those previously discussed herein.

As used herein, the term "substance abuse disorders" includes substance dependence or abuse with or without physiological dependence. The substances associated with these disorders are: alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, marijuana, nicotine, opioids, phencyclidine (or phencyclidine-like compounds), sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of all of the above.

The term "substance abuse disorders" includes drug withdrawal disorders such as alcohol withdrawal with or without perceptual disturbances; alcohol withdrawal delirium; amphetamine withdrawal; cocaine withdrawal; nicotine withdrawal; opioid withdrawal; sedative, hypnotic or anxiolytic withdrawal with or without perceptual disturbances; sedative, hypnotic or anxiolytic withdrawal delirium; and withdrawal symptoms due to other substances. It will be appreciated that reference to treatment of nicotine withdrawal includes the treatment of symptoms associated with smoking cessation.

Other "substance abuse disorders" include substance-induced anxiety disorder with onset during withdrawal; substance-induced mood disorder with onset during withdrawal; and substance-induced sleep disorder with onset during withdrawal.

In particular, compounds of structural formula I are useful for aiding in stopping consumption of tobacco and are useful in treating nicotine dependencies and nicotine withdrawal. The compounds of formula I produce in consumers of nicotine, such as tobacco smokers, a total or partial abstinence from smoking. Further, withdrawal symptoms are lessened and the weight gain that generally accompanies quitting tobacco comsumption is reduced or nonexistent. For smoking cessation, the compound of form I may be used in combination with a nicotine agonist or a partial nicotine agonist such as varenicline, or a monoamine oxidase inhibitor (MAOI), or another active ingredient demonstrating efficacy in aiding cessation of tobacco consumption; for example, an antidepressant such as bupropion, doxepine, ornortriptyline; or an anxiolytic such as buspirone or clonidine.

It will be appreciated that a combination of a conventional antipsychotic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of mania. Such a combination would be expected to provide for a rapid onset of action to treat a manic episode thereby enabling prescription on an "as needed basis". Furthermore, such a combination may enable a lower dose of the antispychotic agent to be used without compromising the efficacy of the antipsychotic agent, thereby minimizing the risk of adverse side-effects. A yet further advantage of such a combination is that, due to the action of the CB1 receptor modulator, adverse side-effects caused by the antipsychotic agent such as acute dystonias, dyskinesias, akathesia and tremor may be reduced or prevented.

Thus, according to a further aspect of the present invention there is provided the use of a CB1 receptor modulator and an antipsychotic agent for the manufacture of a medicament for the treatment or prevention of mania.

The present invention also provides a method for the treatment or prevention of mania, which method comprises administration to a patient in need of such treatment or at risk of developing mania of an amount of a CB1 receptor modulator and an amount of an antipsychotic agent, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CB1 receptor modulator and an antipsychotic agent, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the CB1 receptor modulator and the antipsychotic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of mania. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a CB1 receptor modulator and an antipsychotic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of mania.

The term "combination" also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the antipsychotic agent may be administered as a tablet and then, within a reasonable period of time, the CB1 receptor modulator may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a "fast-dissolving oral formulation" is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about 10 seconds.

Included within the scope of the present invention is the use of CB1 receptor modulators in combination with an antipsychotic agent in the treatment or prevention of hypomania.

It will be appreciated that a combination of a conventional antipsychotic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of schizophrenic disorders. Such a combination would be expected to provide for a rapid onset of action to treat schizophrenic symptoms thereby enabling prescription on an "as needed basis". Furthermore, such a combination may enable a lower dose of the CNS agent to be used without compromising the efficacy of the antipsychotic agent, thereby minimizing the risk of adverse side-effects. A yet further advantage of such a combination is that, due to the action of the CB1 receptor modulator, adverse side-effects caused by the antipsychotic agent such as acute dystonias, dyskinesias, akathesia and tremor may be reduced or prevented.

As used herein, the term "schizophrenic disorders" includes paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; substance-induced psychotic disorder; and psychotic disorder not otherwise specified. Other conditions commonly associated with schizophrenic disorders include self-injurious behavior (e.g. Lesch-Nyhan syndrome) and suicidal gestures.

Suitable antipsychotic agents of use in combination with a CB1 receptor modulator include the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of antipsychotic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include chlorprothixene and thiothixene. Suitable examples of dibenzazepines include clozapine and olanzapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozide. An example of an indolone is molindolone. Other antipsychotic agents include loxapine, sulpiride and risperidone. It will be appreciated that the antipsychotic agents when used in combination with a CB1 receptor modulator may be in the form of a pharmaceutically acceptable salt, for example, chlorpromazine hydrochloride, mesoridazine besylate, thioridazine hydrochloride, acetophenazine maleate, fluphenazine hydrochloride, flurphenazine enathate, fluphenazine decanoate, trifluoperazine hydrochloride, thiothixene hydrochloride, haloperidol decanoate, loxapine succinate and molindone hydrochloride. Perphenazine, chlorprothixene, clozapine, olanzapine, haloperidol, pimozide and risperidone are commonly used in a non-salt form.

Other classes of antipsychotic agent of use in combination with a CB1 receptor modulator include dopamine receptor antagonists, especially D2, D3 and D4 dopamine receptor antagonists, and muscarinic m1 receptor agonists. An example of a D3 dopamine receptor antagonist is the compound PNU-99194A. An example of a D4 dopamine receptor antagonist is PNU-101387. An example of a muscarinic m1 receptor agonist is xanomeline.

Another class of antipsychotic agent of use in combination with a CB1 receptor modulator is the 5-HT_{2A} receptor antagonists, examples of which include MDL100907 and fananserin. Also of use in combination with a CB1 receptor modulator are the serotonin dopamine antagonists (SDAs) which are believed to combine 5-HT_{2A} and dopamine receptor antagonist activity, examples of which include olanzapine and ziperasidone.

Still further, NK-1 receptor antagonists may be favorably employed with the CB1 receptor modulators of the present invention. NK-1 receptor antagonists for use in the present invention are selected from the classes of compounds described previously.

It will be appreciated that a combination of a conventional anti-asthmatic drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of asthma, and may be used for the treatment or prevention of asthma, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anti-asthmatic agent, such that together they give effective relief. Thus, according to a further aspect of the present invention there is provided the use of a CB1 receptor modulator and an anti-asthmatic agent for the manufacture of a medicament for the treatment or prevention of asthma.

Suitable anti-asthmatic agents of use in combination with a compound of the present invention include, but are not limited to: (a) VLA-4 antagonists such as natalizumab and the compounds described in US 5,510,332, WO97/03094, WO97/02289, WO96/40781, WO96/22966, WO96/20216, WO96/01644, WO96/06108, WO95/15973 and WO96/31206; (b) steroids and corticosteroids such as beclomethasone, methylprednisolone, betamethasone, prednisone, dexamethasone, and hydrocortisone; (c) antihistamines (H1-histamine antagonists) such as bromopheniramine, chlorpheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, antazoline, pheniramine pyrilamine, astemizole, terfenadine, loratadine, desloratadine, cetirizine, fexofenadine, descarboethoxyloratadine, and the like; (d) non-steroidal anti-asthmatics including β2-agonists (such as terbutaline, metaproterenol, fenoterol, isoetharine, albuterol, bitolterol, salmeterol, epinephrine, and pirbuterol), theophylline, cromolyn sodium, atropine, ipratropium bromide, leukotriene antagonists (such as zafirlukast, montelukast, pranlukast, iralukast, pobilukast, and SKB-106,203), and leukotriene biosynthesis inhibitors (such as zileuton and BAY-1005); (e) anti-cholinergic agents including muscarinic antagonists (such as ipratropium bromide and atropine); and (f) antagonists of the chemokine receptors, especially CCR-3; and pharmaceutically acceptable salts thereof.

It will be appreciated that a combination of a conventional anti-constipation drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of constipation, or chronic intestinal pseudo-obstruction, and for use for the manufacture of a medicament for the treatment or prevention of constipation or chronic intestinal pseudo obstruction.

The present invention also provides a method for the treatment or prevention of constipation, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an amount of an anti-constipation agent, such that together they give effective relief.

Suitable anti-constipation agents of use in combination with a compound of the present invention include, but are not limited to, osmotic agents, laxatives and detergent laxatives (or wetting agents), bulking agents, and stimulants; and pharmaceutically acceptable salts thereof. A class of osmotic agents can include, but is not limited to, sorbitol, lactulose, polyethylene glycol, magnesium, phosphate, sulfate, and pharmaceutically acceptable salts thereof. A class of laxatives and detergent laxatives, include, but are not limited to, magnesium, docusate sodium, and pharmaceutically acceptable salts thereof. A class of bulking agents include, but are not limited to, psyllium, methylcellulose, calcium polycarbophil, and pharmaceutically acceptable salts thereof. A class of stimulants include, but are not limited to, anthroquinones, and phenolphthalein, and pharmaceutically acceptable salts thereof.

It will be appreciated that a combination of a conventional anti-cirrhosis drug with a CB1 receptor modulator may provide an enhanced effect in the treatment of cirrhosis of the liver, and for use for the manufacture of a medicament for the treatment or prevention of cirrhosis of the liver.

The present invention also provides a method for the treatment or prevention of cirrhosis of the liver, which method comprises administration to a patient in need of such treatment an amount of a compound of the present invention and an anti-cirrhosis agent, such that together they give effective relief.

Suitable anti-cirrhosis agents of use in combination with a compound of the present invention include, but are not limited to, corticosteroids, penicillamine, colchicine, interferon-γ, 2-oxoglutarate analogs, prostaglandin analogs, and other anti-inflammatory drugs and antimetabolites such as azathioprine, methotrexate, leflunamide, indomethacin, naproxen, and 6-mercaptopurine; and pharmaceutically acceptable salts thereof.

The method of treatment of this invention comprises a method of modulating the CB1 receptor and treating CB1 receptor mediated diseases by administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a compound of this invention that selectively antagonizes the CB1 receptor in preference to the other CB or G-protein coupled receptors.

The term "therapeutically effective amount" means the amount the compound of structural formula I that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated. The novel methods of treatment of this invention are for

disorders known to those skilled in the art. The term "mammal" includes humans and companion animals such as dogs and cats.

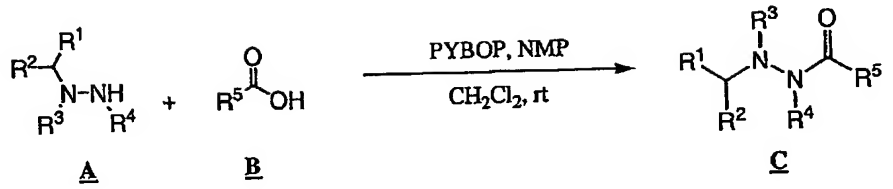
The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with a β-3 agonist the weight ratio of the compound of the Formula I to the β-3 agonist will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

Abbreviations used in the following Schemes and Examples: Ac: acetyl; aq.:aqueous; API-ES: atmospheric pressure ionization-electrospray (mass spectrum term); Boc: tert-butyloxycarbonyl; DEAD: diethyl azodicarboxylate; DMAP: 4-dimethylaminopyridine; DMF: dimethylformamide; DMSO: dimethylsulfoxide; EDC: 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; EPA: ethylene polyacrylamide (a plastic); Et: ethyl ; g: gram; h: hours; Hex: hexane; HOBt: 1-hydroxybenzotriazole; HPLC: high pressure liquid chromatography; HPLC/MS: high pressure liquid chromatography/mass spectrum; *in vacuo:* rotoevaporation; IPAC or IPAc: isopropyl acetate; KHMDS: potassium hexamethyldisilazide; LAH: lithium aluminum hydride; LC: Liquid chromatography; LC/MS, LC-MS: liquid chromatography-mass spectrum; LDA: lithium diisopropyl amide; M: molar; Me: methyl; MHz: megahertz; min: minute; mL: milliliter; mmol: millimole; MS or ms: mass spectrum; MsCl: methanesulfonylchloride; N: normal; $NaBH_3CN$: sodium cyanoborohydride; $NaBH(OAc)_3$: sodium triacetoxyborohydride; NaHMDS: sodium hexamethyldisilazide; NMR: nuclear magnetic resonance; PhH: benzene; PtO_2: platinum dioxide; PyBOP: (benzotriazol-1-yloxy)tripyrrolidino phosphonium hexafluorophosphate; $Rh_2(OAc)_4$: rhodium(II)acetate; R_t: retention time; rt or RT: room temperature; TFA: trifluoroacetic acid; THF: tetrahydrofuran; TLC: thin layer chromatography; TMS-CN: trimethylsilylcyanide.

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative schemes below, therefore, are not limited by the compounds listed or by any particular substitutents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound in place of multiple substituents which are allowed under the definitions of Formula I defined previously.

In order to illustrate the invention, the following schemes and examples are included. These examples do not limit the invention. They are only meant to suggest a method of reducing the invention to practice. Those skilled in the art may find other methods of practicing the invention which are readily apparent to them. However, those methods are also deemed to be within the scope of this invention.

Scheme 1.



A B C

In Scheme 1, an appropriately substituted hydrazine A is reacted with a carboxylic acid B under standard amide bond forming conditions to afford the carboxylic acid hydrazide C. In order to illustrate the invention, the following examples are included. These examples do not limit the invention. They are only meant to suggest a method of reducing the invention to practice. Those skilled in the art may find other methods of practicing the invention which are readily apparent to them. However, those methods are also deemed to be within the scope of this invention.

General Procedures. The LC/MS analyses were preformed using a MICROMASS ZMD mass spectrometer coupled to an AGILENT 1100 Series HPLC utilizing a YMC ODS-A 4.6 x 50 mm column eluting at 2.5 mL/min with a solvent gradient of 10 to 95% B over 4.5 min, followed by 0.5 min at 95% B: solvent A = 0.06% TFA in water; solvent B = 0.05% TFA in acetonitrile. ^{1}H-NMR spectra were obtained on a 500 MHz VARIAN Spectrometer in $CDCl_3$ or CD_3OD as indicated and chemical shifts are reported as δ using the solvent peak as reference and coupling constants are reported in hertz (Hz).

REFERENCE EXAMPLE 1

N-Methyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

Step A N-Methyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of 3-chlorobenzylaldehyde (4.3 mL, 38 mmol) in 100 mL of benzene was added 5 g of 4Å molecular sieves and methylamine (95 mL of 2M solution in THF, 190 mmol). After the reaction mixture was stirred at rt overnight, the molecular sieves was removed by filtration, and concentration of the filtrate afforded the crude imine, which was dissolved in 100 mL of anhydrous THF and was added 4-chlorobenzylmagnesium chloride (0.25M in Et_2O, 168 mL, 42 mmol) via canula at –10 °C. The cooling bath was removed and the reaction was stirred at rt for 1 h. The reaction was quenched with aqueous NH_4Cl, made basic with 2N NaOH, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuum to afford the title compound which was used in the next step without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.32 (s, 1H), 7.24-7.21 (m, 3H), 7.17 (d, 2H), 6.97 (d, 2H), 3.70 (dd, 1H), 3.05 (dd, 1H), 2.82 (dd, 1H), 2.19 (s, 3H). LC-MS: m/e 280 $(M+H)^+$ (2.5 min).

Step B N-nitroso-N-methyl-N-[(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of N-methyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)]ethylamine of Step A and N-chlorosuccinimide (10 g, 76 mmol) in 140 mL of CH_2Cl_2 was added aqueous $NaNO_2$ (10.5 g, 152 mmol in 140 mL of water) and benzyltriethylammonium chloride (34.7 g, 152 mmol). After the reaction was stirred at room temperature overnight, the layers were separated and the organic layer was washed

with water, aqueous sodium bicarbonate, and brine. Then the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 0 to 20% ethyl acetate in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.41-7.36 (m, 3H), 7.32 (s, 1H), 7.24 (d, 2H), 6.92 (d, 2H), 5.85 (dd, 1H), 3.64 (dd, 1H), 3.51 (dd, 1H), 2.86 (s, 3H).

Step C N-Methyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

To a mixture of dichloromethane/diethyl ether (500 mL, 4/1 v/v) was added $TiCl_4$ (19.52 mL, 178 mmol) and magnesium powder (4.33 g, 178 mmol) under N_2. After stirring at room temperature for 2 h, N-nitroso-N-methyl-N-[(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine compound (Step B, 11 g, 35.6 mmol) in 100 mL of ether was added, and the reaction was stirred for another 30 min. The reaction was cooled to 0 °C, and was added dilute HCl (H_2O/concentrated HCl, 40:1 v/v). After stirring for another 2 h, the resulting purple solution was made alkaline by the addition of 2 N NaOH and was extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 30 to 60% ethyl acetate in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.32-7.26 (m, 3H), 7.23 (s, 1H), 7.12 (d, 2H), 6.94 (d, 2H), 3.61 (dd, 1H), 3.42 (dd, 1H), 2.93 (dd, 1H), 2.39 (s, 3H). LC-MS: m/e 295 $(M + H)^+$ (2.6 min).

REFERENCE EXAMPLE 2

N-Methyl-N-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

The title compound was prepared by the same procedure described in Reference Example 1 substituting 3-chlorobenzylaldehyde with 3-bromobenzylaldehyde in Step A.
LC-MS: m/e 340 $(M + H)^+$ (3.0 min).

REFERENCE EXAMPLE 3

N-Ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

Step A N-Ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of 3-chlorobenzylaldehyde (42.3 mL, 20 mmol) in 50 mL of benzene was added 5 g of 4Å molecular sieves and ethylamine (50 mL of 2 M solution in THF, 100 mmol). After the reaction mixture was stirred at rt overnight, the molecular sieves were removed by filtration, and the filtrate was concentrated to give the crude imine, which was dissolved in 60 mL of anhydrous THF. 4-chlorobenzylmagnesium chloride (0.25M in Et_2O, 120 mL, 30 mmol) was added at –10 °C. The cooling bath was removed and the reaction was stirred at rt for 1h. The reaction was quenched with aqueous NH_4Cl, made basic with 2N NaOH, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuum to afford the title compound which was used in the next step without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.33 (s, 1H), 7.24-7.21 (m, 3H), 7.18 (d, 2H), 6.98 (d, 2H), 3.81 (dd, 1H), 3.06 (dd, 1H), 2.81 (dd, 1H), 2.42 (m, 2H), 1.03 (t, 3H).

Step B N-nitroso-N-ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of N-ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)]ethylamine Step A and N-chlorosuccinimide (5.34 g, 40 mmol) in 70 mL of CH_2Cl_2 was added aqueous $NaNO_2$ (5.52 g, 80 mmol of $NaNO_2$ in 70 mL of water) and benzyltriethylammonium chloride (18.2 g, 80 mmol). After the reaction was stirred for 48 hours, the layers were separated and the organic layer was washed with water, aqueous sodium bicarbonate, and brine. Then the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 0 to 15% ethyl acetate in hexane to give the title compound. ^1H NMR (500 MHz, CD_3OD): δ 7.42 (s, 1H), 7.39-7.33 (m, 3H), 7.24 (d, 2H), 7.21 (d, 2H), 5.62 (dd, 1H), 3.70(m, 2H), 3.43 (dd, 1H), 3.22 (dd, 1H), 0.72 (t, 3H). LC-MS: m/e 323 $(M + H)^+$ (4.2 min).

Step C N-Ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

To a mixture of dichloromethane/diethyl ether (250 mL, 4/1 v/v) was added $TiCl_4$ (8.7 mL, 79 mmol) and magnesium powder (1.92 g, 79 mmol) under N_2. After stirring at rt for 2 h, N-nitroso-N-ethyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine of Step B (5.1 g, 15.8 mmol) in 50 mL of diethyl ether was added, and the reaction was stirred for 30 min. The reaction was cooled to 0 °C and was added dilute HCl. After stirring for another hour, the resulting purple solution was made alkaline by the addition of 2N NaOH and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 20 to 50% ethyl acetate in hexane to give the title compound. ^1H NMR (500 MHz, CD_3OD): δ 7.40 (s, 1H), 7.35-7.21 (m, 3H), 7.21 (s, 4H), 4.41 (dd, 1H), 3.63 (dd, 1H), 3.20 (m, 2H), 3.12 (dd, 1H), 0.87 (t, 3H).

REFERENCE EXAMPLE 4

N-Allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

Step A N-Allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of 3-chlorobenzylaldehyde (3.4 mL, 30 mmol) in 100 mL of benzene was added 8 g of 4Å molecular sieves and allylamine (11.3 mL, 150 mmol). After stirring at rt overnight, the molecular sieves was removed by filtration, and the filtrate was concentrated to give the crude imine, which was dissolved in 100 mL of anhydrous THF and was added 4-chlorobenzylmagnesium chloride (0.25M in Et_2O, 180 mL, 45 mmol) at –10 °C. The cooling bath was removed and the reaction was stirred at rt for 1 h. The reaction was quenched with aqueous NH_4Cl, made basic with 2N NaOH, and extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuum to afford the title compound which was used in the next step without further purification. ^1H NMR (500 MHz, CD_3OD): δ 7.33 (s, 1H), 7.21 (m, 3H), 7.18 (d, 2H), 6.98 (d, 2H), 5.80 (m, 1H), 5.04 (s, 1H), 5.02 (d, 1H), 3.82 (dd, 1H), 3.03 (dd, 1H), 2.98 (dd, 1H), 2.82 (dd, 1H).

Step B N-nitroso-N-allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine

To a solution of N-allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)]ethylamine of Step A and N-chlorosuccinimide (8 g, 60 mmol) in 100 mL of CH_2Cl_2 was added aqueous $NaNO_2$ (8.28 g, 120 mmol

of $NaNO_2$ in 100 mL of water) and benzyltriethylammonium chloride (27.4 g, 120 mmol). After the reaction was stirred at room temperature for 48 hours, the layers were separated and the organic layer was washed with water, aqueous sodium bicarbonate, and brine. Then the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 0 to 15% ethyl acetate in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.41 (s, 1H), 7.18-7.11 (m, 3H), 7.21 (d, 2H), 7.20 (d, 2H), 5.58 (dd, 1H), 5.38 (m, 1H), 4.96 (d, 1H), 4.83 (s, 1H), 4.37 (dd, 1H), 3.77 (m, 2H), 3.43 (dd, 1H). LC-MS: m/e 335 $(M + H)^+$ (4.3 min).

Step C N-Allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine

To a mixture of dichloromethane/diethyl ether (250 mL, 4/1 v/v) was added $TiCl_4$ (8.7 mL, 79 mmol) and magnesium power (1.92 g, 79 mmol) under N_2. After stirring at rt for 2 h, N-nitroso-N-allyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]amine of Step B (5.3 g, 15.8 mmol) in 50 mL of ether was added, and the reaction was stirred for another 30 min. The reaction was cooled to 0 °C, and was added dilute HCl (H_2O/concentrated HCl, 40:1 v/v). After stirring for another hour, the resulting purple solution was made alkaline by the addition of 2N NaOH and extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 20 to 30% ethyl acetate in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.24 (s, 1H), 7.23-7.20 (m, 3H), 7.13 (d, 2H), 6.98 (d, 2H), 5.84 (m, 1H), 5.19 (s, 1H), 5.18 (d, 1H), 3.80 (dd, 1H), 3.43 (dd, 1H), 3.17 (dd, 1H), 3.03 (dd, 1H), 2.96 (dd, 1H). LC-MS: m/e 321 $(M + H)^+$ (3.4 min).

REFERENCE EXAMPLE 5

2-(2-Fluorophenyloxy)-2-methylpropionic acid

Step A 2-(2-Fluorophenyloxy)-2-methylpropionic acid

To a solution of 2-fluorophenol (2.0 g, 18 mmol) and 1,1,1-trichloro-2-methyl-2-propanol (7.9 g, 45 mmol) in acetone (100 mL) was added sodium hydroxide (7.1 g, 0.18 mol), and an ice-water bath was periodically applied to maintain a gentle reflux. After the reflux subsided, the reaction was stirred for one additional hour. The volatile materials were removed on a rotary evaporator, and the residue partitioned between ether (100 mL), hexane (100mL) and water (200 mL). The aqueous layer was separated and acidified with concentrated hydrochloric acid (pH = 2), and extracted with ether (3 x 100 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 7.15-7.05 (m, 4H), 1.56 (s, 6H). LC-MS: m/e 199 $(M + 1)^+$ (2.3 min).

The acids of Reference Examples 6 and 7 were prepared following the procedures described for Reference Example 5 substituting 2-fluorophenol with appropriately substituted phenols.

REFERENCE EXAMPLE 6

2-(3-Chlorophenyloxy)-2-methylpropionic acid

^{1}H NMR (500 MHz, CD_3OD): δ 7.23 (t, 1H), 7.00 (dd, 1H), 6.93 (t, 1H), 6.84 (dd, 1H), 1.59 (s, 6H).

LC-MS: m/e 215 $(M + 1)^+$, (2.7 min).

REFERENCE EXAMPLE 7

2-(3,5-Dichlorophenyloxy)-2-methylpropionic acid

^{1}H NMR (500 MHz, CD_3OD): δ 7.05 (t, 1H), 6.84 (d, 2H), 1.60 (s, 6H).

REFERENCE EXAMPLE 8

2-(2-Pyridyloxy)-2-methylbutanoic acid.

Step A Benzyl 2-(2-Pyridyloxy)propionate

To a mixture of 2-hydroxypyridine (2.9 g, 30 mmol), benzyl lactate (5.0 g, 21 mmol) and triphenylphosphine (12 g, 47 mmol) in 100 mL CH_2Cl_2 was added diethylazodicarboxylate (7.8 mL, 45 mmol) at 0°C. The reaction was allowed to warm to room temperature for 4 h. The resulting mixture was diluted with hexane (100 mL) and concentrated with 20 g silica gel. The material was loaded onto a silica gel column, which was eluted with 10% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.00 (dd, 1H), 7.68 (ddd, 1H), 7.36-7.28 (m, 5 H), 6.94 (dd, 1H), 6.84 (dd, 1H), 5.30 (q, 1H), 5.18 (s, 2H), 1.59 (d, 3H). LC-MS: m/e 258 $(M + H)^+$ (3.3 min).

Step B Benzyl 2-(2-Pyridyloxy)-2-methylbutanoate.

To a solution of benzyl 2-(2-pyridyloxy)propionate (1.6 g, 6.2 mmol) and ethyl iodide (1.5 mL, 25 mmol) in 10 mL anhydrous THF at –78°C was added sodium hexamethyldisilazide (1 M in THF, 9.3 mL, 9.3 mmol) (potassium hexamethyldisilazide in toluene may be used with similar results). The reaction was allowed to warm to room temperature over 2 h and was partitioned between saturated ammonium chloride (100 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.87 (dd, 1H), 7.63 (ddd, 1H), 7.27 (m, 3H), 7.18. (m, 2H), 6.85 (dd, 1H), 6.74 (dd, 1H), 5.08 (ABq, 2H), 2.13 (m, 1H), 1.94 (m, 1H), 1.65 (s, 3H), 0.95 (t, 3H). LC-MS: m/e 286 $(M + H)^+$ (3.8 min).

Step C 2-(2-Pyridyloxy)-2-methylbutanoic Acid

A mixture of benzyl 2-(2-pyridyloxy)-2-methylbutanoate (1.6 g, 5.5 mmol) and 10% palladium on carbon (50 mg) in 50 mL MeOH was degassed and filled with hydrogen using a balloon. After stirring at room temperature overnight, the reaction mixture was filtered through CELITE diatomaceous earth and washed with MeOH (20 mL), and the filtrate was concentrated to dryness to give the title

compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.03 (dd, 1H), 7.64 (ddd, 1H), 6.89 (dd, 1H), 6.76 (dd, 1H), 2.14 (m, 1H), 1.94 (m, 1H), 1.64 (s, 3H), 0.99 (t, 3H). LC-MS: m/e 196 $(M + H)^+$ (1.8 min).

REFERENCE EXAMPLE 9

2-(2-Pyridyloxy)-2-methylpropionic Acid

The title compound was prepared following the procedures described for Reference Example 8 substituting ethyl iodide and sodium hexamethyldisilazide with methyl iodide and potassium hexamethyldisilazide respectively at Step B. ^{1}H NMR (500 MHz, CD_3OD): δ 8.04 (dd, 1H), 7.64 (ddd, 1H), 6.89 (dd, 1H), 6.76 (dd, 1H), 1.66 (s, 6H). LC-MS: m/e 182 $(M + H)^+$ (1.5 min).

REFERENCE EXAMPLE 10

2-Methyl-2-(5-chloro-2-pyridyloxy)propionic acid

Step A Ethyl 2-Methyl-2-(5-chloro-2-pyridyloxy)propionate

A mixture of 5-chloro-2-hydroxypyridine (5.0 g, 39 mmol), ethyl 2-bromoisobutyrate (5.7 mL, 39 mmol) and cesium carbonate (25 g, 77 mmol) in 50 mL acetonitrile was heated at 50°C overnight. The volatile materials were removed by concentrating on a rotary evaporator, and the residue was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 5% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.99 (d, 1H), 7.67 (dd, 1H), 6.68 (d, 1H), 4.13 (q, 2H), 1.64 (s, 6H), 1.14 (t, 3H). LC-MS: m/e 244 $(M + H)^+$ (3.41 min).

Step B 2-Methyl-2-(5-chloro-2-pyridyloxy)propionic Acid

A mixture of ethyl 2-methyl-2-(5-chloro-2-pyridyloxy)propionate and sodium hydroxide (0.85 g, 21 mmol) in 15 mL acetonitrile and 15 mL water was heated at 50°C overnight. The volatile materials were removed by concentrating on a rotary evaporator, and the residue was partitioned between 2 M hydrochloric acid (100 mL) and ether (100 mL). The organic layer was separated and washed with water (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.02 (d, 1H), 7.65 (dd, 1H), 6.77 (d, 1H), 1.62 (s, 6H). LC-MS: m/e 216 $(M + H)^+$ (2.33 min).

REFERENCE EXAMPLE 11

2-Methyl-2-(5-trifluoromethyl-2-pyridyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 10 substituting 5-chloro-2-hydroxypyridine with 5-trifluoromethyl-2-hydroxpyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.38 (br s, 1H), 7.93 (dd, 1H), 7.13 (d, 1H), 1.70 (s, 6H). LC-MS: m/e 250 $(M + H)^+$ (2.6 min).

REFERENCE EXAMPLE 12

2-Methyl-2-(6-methyl-2-pyridyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 10 substituting 5-chloro-2-hydroxpyridine with 6-methyl-2-hydroxpyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 7.51 (t, 1H), 6.74 (d, 1H), 6.53 (d, 1H), 2.34 (s, 3H), 1.64 (s, 6H). LC-MS: m/e 196 $(M + H)^+$ (1.3 min).

REFERENCE EXAMPLE 13

2-Methyl-2-(2-pyrimidyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 10 substituting 5-chloro-2-hydroxpyridine with 2-hydroxpyrimidine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.53 (d, 2H), 7.09 (t, 1H), 1.74 (s, 6H).

REFERENCE EXAMPLE 14

2-Methyl-2-(4-trifluoromethyl-2-pyridyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 10 substituting 5-chloro-2-hydroxpyridine with 4-trifluoromethyl-2-hydroxpyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.30 (d, 1H), 7.18 (d, 1H), 7.05 (s, 1H), 1.71 (s, 6H).

REFERENCE EXAMPLE 15

2-Methyl-2-(6-trifluoromethyl-4-pyrimidyloxy)propionic Acid

The title compound was prepared following the procedures described for Reference Example 10 substituting 5-chloro-2-hydroxpyridine with 6-trifluoromethyl-4-hydroxpyrimidine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 8.81 (s, 1H), 7.28 (s, 1H), 1.75 (s, 6H). LC-MS: m/e 251 $(M + H)^+$ (2.1 min).

REFERENCE EXAMPLE 16

2-Methyl-2-(5-methyl-2-pyridyloxy)propionic acid

The title compound was prepared from 5-methyl-2-hydroxypyridine following the procedure described for Reference Example 10. ^{1}H NMR (500 MHz, CD_3OD): δ 7.85 (s, 1H), 7.47 (dd, 1H), 6.65 (d, 1H), 2.22 (s, 3H), 1.62 (s, 6H). LC-MS: m/e 196 $(M + H)^+$ (2.3 min).

REFERENCE EXAMPLE 17

2-Methyl-2-(5-cyano-2-pyridyloxy)propionic Acid

Step A Methyl 2-methyl-2-(5-cyano-2-pyridyloxy)propionate

To a solution 2-methyl-2-(5-chloro-2-pyridyloxy)propionic acid (Reference Example 11, 1.0 g, 4.6 mmol) in dichloromethane (10 mL) and methanol (10 mL) at 0°C was added trimethylsilyldiazomethane (2 M in hexane) until a yellow color persisted. After stirring at room temperature for 15 min, the reaction mixture was concentrated to dryness to give the crude methyl ester,

which was used without further purification. Thus, the crude methyl ester was dissolved in acetonitrile (5 mL), and was added potassium cyanide (0.45 g, 7.0 mmol), tributyltin chloride (0.10 mL, 0.37 mmol). The mixture was degassed and was added tris(dibenzylideneacetone)dipalladium (0.15 g, 0.16 mmol) and tri(tert-butyl)phosphine (10% weight, 2.2 mL, 0.84 mmol), and was degassed two more times. After heating at 80°C overnight. The reaction mixture was cooled to room temperature, diluted with dimethyl sulfoxide (5 mL) and water (2 mL) and filtered. The filtrate was loaded onto a reverse phase HPLC column eluting with 20 to 100% water in acetonitrile to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.43 (d, 1H), 7.97 (dd, 1H), 6.91 (d, 1H), 3.63 (s, 3H), 1.66 (s, 6H).

Step B 2-Methyl-2-(5-cyano-2-pyridyloxy)propionic Acid

To a solution of methyl 2-methyl-2-(5-cyano-2-pyridyloxy)propionate (12 mg) in tetrahydrofuran (2 mL) and water (1 mL) was added lithium hydroxide monohydrate (10 mg). After stirring at room temperature overnight, the reaction mixture was acidified with 1 N hydrochloric acid, and the resulting mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered and concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.23 (d, 1H), 7.96 (dd, 1H), 6.91 (d, 1H), 1.64 (s, 6H).

REFERENCE EXAMPLE 18

2-Methyl-2-(5-fluoro-2-pyridyloxy)propionic Acid

Step A Benzyl 2-(5-Fluoro-2-pyridyloxy)propionate

To a mixture of 5-fluoro-2-hydroxypyridine (2.0 g, 18 mmol), benzyl lactate (3.2 g, 18 mmol) and triphenylphosphine (9.3 g, 35 mmol) in 50 mL of CH_2Cl_2 was added diisopropylazodicarboxylate (7.0 mL, 35 mmol) at 0°C. The reaction was allowed to warm to room temperature overnight. The resulting mixture was loaded onto a silica gel column, which was eluted with 0 to 25% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.81 (d, 1H), 7.50 (ddd, 1H), 7.36–7.26 (m, 5H), 6.85 (dd, 1H), 5.24 (q, 1H), 5.16 (ABq, 2H) 1.55 (d, 3H). LC-MS: m/e 276 $(M + H)^+$ (3.6 min).

Step B Benzyl 2-(5-Fluoro-2-pyridyloxy)-2-methylpropionate

To a solution of benzyl 2-(5-fluoro-2-pyridyloxy)propionate (2.9 g, 10 mmol) and methyl iodide (3.3 mL, 53 mmol) in 40 mL of anhydrous THF at –78°C was added potassium hexamethyldisilazide (0.5 M in toluene, 32 mL, 16 mmol). The reaction was allowed to warm to room temperature over 3 h and was partitioned between saturated ammonium chloride (150 mL) and EtOAc (150 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness, and the residue was purified by flash column chromatography on silica gel eluted with 0 to 20% EtOAc in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.63 (d, 1H), 7.44 (ddd, 1H), 7.27 (m, 3H), 7.18 (m, 2H), 6.74 (dd, 1H), 5.09 (s, 2H) 1.64 (s, 6H). LC-MS: m/e 290 $(M + H)^+$ (3.7 min).

Step C 2-(5-Fluoro-2-pyridyloxy)-2-methylpropionic Acid

A mixture of benzyl 2-(5-fluoro-2-pyridyloxy)-2-methylpropionate (2.6 g, 9.2 mmol) and 10% palladium on carbon (0.26 mg) in 20 mL MeOH was degassed and filled with hydrogen using a balloon. After stirring at room temperature for 3 h, the reaction mixture was filtered through CELITE diatomaceous earth and washed with MeOH (20 mL), and the filtrate was concentrated to dryness to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 7.91 (d, 1H), 7.48 (ddd, 1H), 6.78 (dd, 1H), 1.65 (s, 6H). LC-MS: m/e 200 $(M + H)^+$ (2.6 min).

REFERENCE EXAMPLE 19

2-Methyl-2-(4-methyl-2-pyridyloxy)propionic Acid

2-Methyl-2-(4-methyl-2-pyridyloxy)propionic Acid was prepared following the procedures described for Reference Example 17 substituting 5-fluoro-2-hydroxypyridine with 4-methyl-2-hydroxypyridine at Step A. ^{1}H NMR (500 MHz, CD_3OD): δ 7.88 (d, 1H), 6.73 (d, 1H), 6.57 (s, 1H), 2.28 (s, 3H), 1.63 (s, 6H).

REFERENCE EXAMPLE 20

2-Methyl-2-(5-difluoromethyl-2-pyridyloxy)propionic Acid

Step A 4-Chloro-3-pyridinecarboxaldehyde

To a solution of 2-chloro-5-iodopyridine (18 g, 75 mmol) in ether (100 mL) and tetrahydrofuran (100 mL) at -78°C was added *tert*-butyllithium (1.7 M in pentane, 60 mL, 100 mmol). After stirring at -78°C for 30 min, DMF (11 mL, 150 mmol) was added, and the reaction was allowed to warm up to 0°C over 30 min, and was poured into a stirred mixture of ice (200 g), concentrated hydrochloric acid (20 mL) and ether (200 mL). The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 0 to 10% ether in hexane/dichloromethane (1:1) to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): 10.18 (s, 1H), 8.90 (s, 1H), 8.17 (d, 1H), 7.55 (d, 1H).

Step B 4-Chloro-3-difluoromethylpyridine

To a solution of 4-chloro-3-pyridinecarboxaldehyde (3.7 g, 26 mmol) in 15 mL of dichloromethane at –78°was added (dimethylamino)sulfur trifluoride (15 mL, 0.15 mol), and the reaction was allowed to warm up to room temperature overnight. The reaction was quenched by carefully transferring into a mixture of ice (100 g) and sodium sulfite (10 g). The product was extracted with ether (100 mL x 2), and the combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with 0 to 10% ether in hexane to give the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.59 (s, 1H), 7.84 (d, 1H), 7.48 (d, 1H), 6.74 (t, 1H).

Step C 2-Methyl-2-(5-difluoromethyl-2-pyridyloxy)propionic Acid

The title compound (1.6 g) was prepared from 4-chloro-3-difluoromethylpyridine (3.0 g) following the procedure described for Reference Example 15 with the following modifications. The ester intermediate was purified by flash column chromatography on silica gel eluting with 0 to 10% ether in hexane. The hydrolysis of the ester to the title compound was effected with lithium hydroxide in methanol/tetrahydrofuran/water. ^{1}H NMR (500 MHz, CD_3OD): δ 8.22 (d, 1H), 7.82 (dd, 1H), 6.88 (d, 1H), 6.77 (t, 1H), 1.64 (s, 6H).

REFERENCE EXAMPLE 21

1-Methylcyclobutanecarboxylic Acid

Step A Ethyl 1-Methylcyclobutanecarboxylic Acid

To a solution of ethyl cyclobutanecarboxylate (1.0 g, 7.8 mmol) and methyl iodide (2.4 mL, 39 mmol) in 20 mL of anhydrous tetrahydrofuran at -78°C was added potassium hexamethyldisilazide (0.5 M in toluene, 23 mL, 12 mmol), and the reaction was allowed to warm to room temperature overnight. After quenching with saturated ammonium chloride (10 mL), the resulting mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 4.12 (q, 2H), 2.5-1.8 (m, 6H), 1.48 (s, 3H), 1.25 (t, 3H).

Step B 1-Methylcyclobutanecarboxylic Acid

To a solution of ethyl 1-methylcyclobutanecarboxylate (Step A, 1.0 g, 7.0 mmol) in water (10 mL) and dioxane (10 mL) was added lithium hydroxide monohydrate (2 g, 48 mmol), and the mixture was heated at 100°C for 2 days. After cooling to room temperature, the reaction was quenched with 2 M hydrochloric acid to pH = 2, and the resulting mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic layer was separated, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (500 MHz, CD_3OD): δ 2.5-1.8 (m, 6H), 1.39 (s, 3H).

REFERENCE EXAMPLE 22

1-Ethylcyclobutanecarboxylic Acid

The title compound was prepared following the same procedure as described for Reference Example 9 substituting methyl iodide with ethyl iodide. ^{1}H NMR (500 MHz, CD_3OD): δ 2.44-2.34 (m, 2H), 1.96-1.84 (m, 4H), 1.81 (q, 2H), 0.84 (t, 3H).

REFERENCE EXAMPLE 23

1-Propylcyclobutanecarboxylic Acid

The title compound was prepared following the same procedure as described for Reference Example 9 substituting methyl iodide with propyl iodide. ^{1}H NMR (500 MHz, CD_3OD): δ 2.46-2.34 (m, 2H), 1.96-1.84 (m, 4H), 1.78-1.70 (m, 2H), 1.30-1.20 (m, 2H), 0.92 (t, 3H).

REFERENCE EXAMPLE 24

1-Isopropylcyclobutanecarboxylic Acid

The title compound was prepared following the same procedure as described for Reference Example 9 substituting methyl iodide with isopropyl iodide at Step A and potassium hydroxide in dimethylsulfoxide and water for lithium hydroxide in dioxane and water. ^{1}H NMR (500 MHz, CD_3OD): δ 2.7-1.7 (m, 7 H), 0.93 (d, 6H).

REFERENCE EXAMPLE 25

1-Benzylcyclobutanecarboxylic Acid

The title compound was prepared following the same procedure as described for Reference Example 9 substituting methyl iodide with benzyl bromide. ^{1}H NMR (500 MHz, CD_3OD): δ 7.26-7.14 (m, 5H), 3.09 (s, 2H), 2.42-2.34 (m, 2H), 2.11-2.04 (m, 2H), 1.95-1.83 (m, 2H).

REFERENCE EXAMPLE 26

1-Phenylcyclobutanecarboxylic Acid

A mixture of 1-phenylcyclobutanecarbonitrile (5.0 g, 32 mmol) in water (50 mL) and concentrated hydrochloric acid (50 mL) was heated at 100°C for 3 h. After cooling to room temperature, the product was extracted with ethyl acetate (2x50 mL), and the ethyl acetate solution was back extracted with 2 M aqueous sodium hydroxide (2x50 mL). The aqueous extracts were neutralized with concentrated hydrochloric acid (pH = 2), and the product was extracted with ethyl acetate (2 x 50 mL). The organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to dryness to give the title compound as a white solid (0.66 g). ^{1}H NMR (500 MHz, CD_3OD): δ 7.40-7.18 (m, 5H), 2.86-2.75 (m, 2H), 2.54-2.43 (m, 2H), 2.08-1.98 (m, 1H), 1.90-1.80 (m, 1H).

REFERENCE EXAMPLE 27

1-tert-Butoxycarbonyl-3-ethylazetidine-3-carboxylic Acid

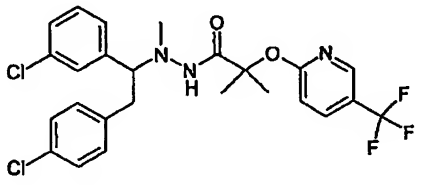
Step A Methyl 1-tert-Butoxycarbonylazetidine-3-carboxylate

To a solution of 1-tert-butoxycarbonylazetidine-3-carboxylic acid (0.90 g, 4.5 mmol) in methanol (10 mL) and methylene chloride (10 mL) at 0°C was added trimethylsilyldiazomethane (2 M in hexane, 4 mL, 7.0 mmol) until a yellow color persisted. The reaction was stirred at room temperature for 10 min, and was concentrated to dryness to give the title compound, which was used without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ 4.15 (d, 2H), 3.76 (s, 3H), 3.72 (d, 2H), 1.94 (q, 2H), 1.42 (s, 9H), 0.88 (t, 3H). LC-MS: m/e 266 $(M+Na)^+$.

Step B 1-tert-Butoxycarbonyl-3-ethylazetidine-3-carboxylic Acid

The title compound was prepared following the procedure described for Reference Example 10 substituting cyclobutanecarboxylate with methyl 1-tert-butoxycarbonylazetidine-3-carboxylate. ^{1}H NMR (500 MHz, CD_3OD): δ 4.12 (d, 2H), 3.70 (d, 2H), 1.82 (q, 2H), 1.42 (s, 9H), 0.90 (t, 3H).

EXAMPLE 1



N'-[1-(3-Chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[5-(trifluoromethylpyridin-2-yl)oxy]propanoyl}hydrazide

To a solution of N-methyl-N-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]hydrazine (Reference Example 1, 295 mg, 1 mmol) and 2-methyl-2-(5-trifluoromethyl-2-pyridyloxy)propionic Acid (Reference Example 11, 299 mg, 1.2 mmol) in 4 mL of dichloromethane was added PyBop (1.04 g, 2 mmol) and N-methylmorpholine (0.329 mL, 3 mmol). After stirring at rt overnight, the reaction mixture was loaded onto a silica column eluting with 20-30% EtOAc in hexanes to afford the title compound. ^{1}H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.18 (s, 1H), 7.15 (m, 1H), 7.12 (dd, 1H), 7.05 (d, 2H), 7.01 (d, 1H), 6.95 (d, 1H), 6.71 (d, 2H), 3.82 (dd, 1H), 3.23 (dd, 1H), 2.71 (dd, 1H), 2.41 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H). LC-MS: m/e 526 $(M + H)^+$ (4.2 min).

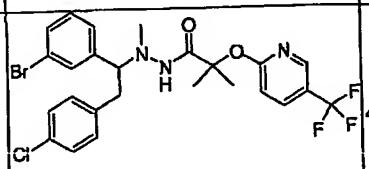
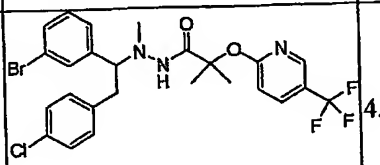
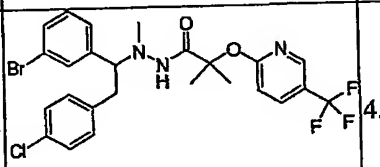
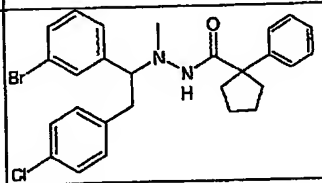
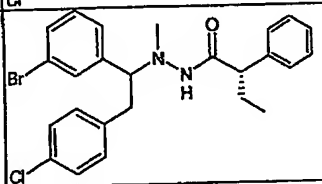
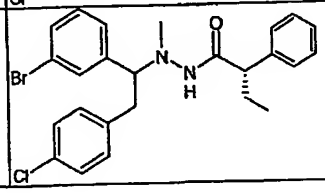
The material described above was separated into two pure enantiomers by eluting on a Chiralpak AD column.

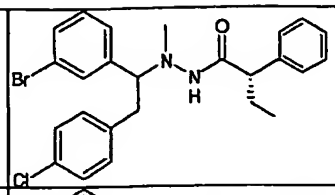
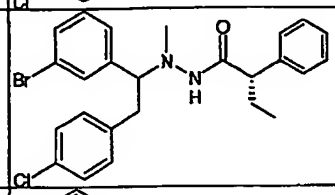
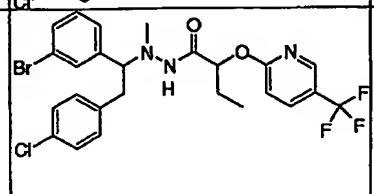
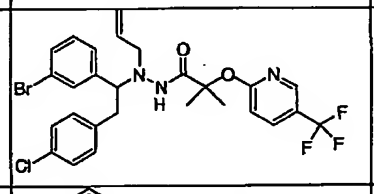
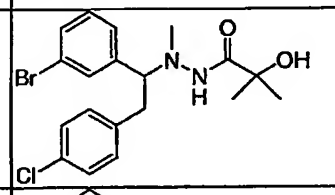
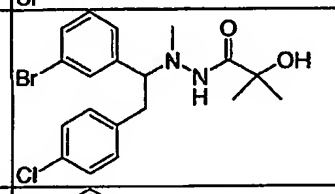
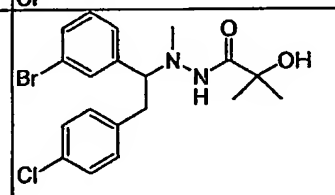
Slower eluting isomer: retention time 8.9 min (flow rate = 0.75 mL/min, 7% EtOH in hexane). ^{1}H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.18 (s, 1H), 7.15 (m, 1H), 7.12 (dd, 1H), 7.05 (d, 2H), 7.01 (d, 1H), 6.95 (d, 1H), 6.71 (d, 2H), 3.82 (dd, 1H), 3.23 (dd, 1H), 2.71 (dd, 1H), 2.41 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H). LC-MS: m/e 526 $(M + H)^+$ (4.2 min).

Faster eluting isomer: retention time 6.6 min (flow rate = 0.75 mL/min, 7% EtOH in hexane). ^{1}H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.18 (s, 1H), 7.15 (m, 1H), 7.12 (dd, 1H), 7.05 (d, 2H), 7.01 (d, 1H), 6.95 (d, 1H), 6.71 (d, 2H), 3.82 (dd, 1H), 3.23 (dd, 1H), 2.71 (dd, 1H), 2.41 (s, 3H), 1.63 (s, 3H), 1.55 (s, 3H). LC-MS: m/e 526 $(M + H)^+$ (4.2 min).

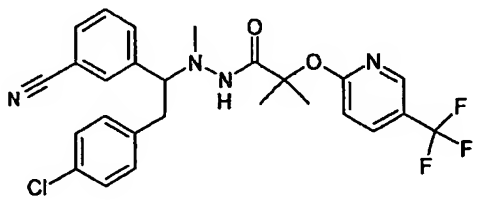
Compounds of Examples 2-13 (Table 1) were prepared from hydrazines of Reference Example 2-4 and the appropriate carboxylic acid of Reference Examples or commercial sources following the procedures described in Example 1.

Table 1.

Ex. No.	Name	Structure	Retention Time (min.)	HPLC-mass spectrum *m/e*
2.	N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide		4.2	570
3.	Faster eluting isomer: N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hyrazide		4.2	570
4.	Slower eluting isomer: N'-[1-(3-bromophenyl)-2-(4-chlorophenyl) ethyl]-N'-methyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide		4.2	570
5.	N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(1-phenylcyclopentanecarboxyl) hydrazide		4.7	511
6.	Faster eluting isomer: N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide		4.1	485
7.	Slower eluting isomer: N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide		4.1	485

8.	Faster eluting isomer: N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenybutanoyl]hydrazide		4.1	441
9.	Faster eluting isomer: N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide		4.1	441
10.	N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-[5-trifluoromethypyridin-2-yl)oxy]butanoyl}hydrazide		4.3	526
11.	N'[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-allyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide		4.6	552
12.	N'-{1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(2-methyl-2-hydroxypropanoyl) hydrazide		3.4	381
13.	Faster eluting isomer: N'-[1-(3-chlorophenyl-2-(4-chlorophenyl) ethyl]-N'-methyl-N-(2-methyl-2-hydroxypropanoyl)hydrazide		3.4	381
14.	Slower eluting isomer: N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(2-methyl-2-hydroxypropanoyl)hydrazide		3.4	381

EXAMPLE 15

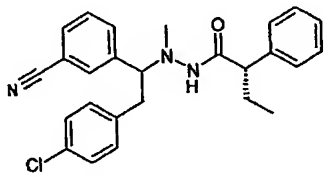


N'-[1-(3-Cyanophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[(5-trifluoromethylpyridin-2-yl)oxy]propanoyl}hydrazide

N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[(5-trifluoromethylpyridin-2-yl)oxy]propanoyl}hydrazide (Example 2, 100 mg, 0.175 mmol), sodium cyanide (8.6 mg, 0.175 mmol), and 18-crown-6 (46.2 mg, 0.175 mmol) were charged into a 5 mL round bottom flask, to which was added 2 mL of anhydrous 1,4-dioxane followed by $Pd(PPh_3)_4$ (101 mg,0.0875 mmol). After stirring at 100 °C overnight, the reaction was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$ and concentrated to dive the crude product, which was purified by silica column eluting with 20-50% EtOAc in hexanes to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.51 (dd, 1H), 7.49 (s, 1H), 7.33 (m, 2H), 7.06 (d, 2H), 7.00 (d, 1H), 6.71 (d, 2H), 3.91 (dd, 1H), 3.26 (dd, 1H), 2.69 (dd, 1H), 2.42 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H). LC-MS: m/e 517 $(M + H)^+$ (3.9 min).

The material described above was separated into pure enantiomers by eluting on a Chiralpak AD column. Faster eluting isomer: retention time 8.4 min (flow rate 0.75 ml/min, 8% EtOH in hexane). ^1H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.51 (dd, 1H), 7.49 (s, 1H), 7.33 (m, 2H), 7.06 (d, 2H), 7.00 (d, 1H), 6.71 (d, 2H), 3.91 (dd, 1H), 3.26 (dd, 1H), 2.69 (dd, 1H), 2.42 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H). LC-MS: m/e 517 $(M + H)^+$ (3.9 min). Slower eluting isomer: retention time 10.4 min (flow rate 0.75 ml/min, 8% EtOH in hexane). ^1H NMR (500 MHz, CD_3OD): δ 8.30 (bs, 1H), 7.96 (dd, 1H), 7.51 (dd, 1H), 7.49 (s, 1H), 7.33 (m, 2H), 7.06 (d, 2H), 7.00 (d, 1H), 6.71 (d, 2H), 3.91 (dd, 1H), 3.26 (dd, 1H), 2.69 (dd, 1H), 2.42 (s, 3H), 1.62 (s, 3H), 1.52 (s, 3H). LC-MS: m/e 517 $(M + H)^+$ (3.9 min).

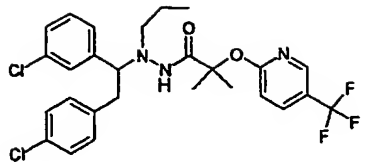
EXAMPLE 16



N'-[1-(3-Cyanophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2*S*)-phenylbutanoyl]hydrazide

The title compounds were prepared from the respective isomers of N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2*S*)-phenylbutanoyl]hydrazide (Example 6 and 7) following the procedure described in Example 15. Faster eluting isomer: LC-MS: m/e 432 $(M + H)^+$ (3.8 min). Slower eluting isomer: LC-MS: m/e 432 $(M + H)^+$ (3.8 min).

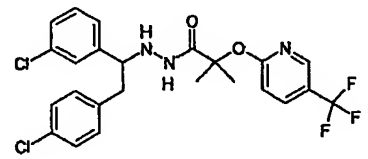
EXAMPLE 17



N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-propyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide

A mixture of N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-allyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide (Example 11, 150 mg, 0.27 mmol), 4 mL of EtOAc, 0.5 mL of EtOH, and PtO_2 (15 mg) was stirred under a H_2 balloon at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was concentrated to dryness. The residue was purified by flash column chromatography on a silica column eluting with 10-30% EtOAc in hexanes to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.29 (s, 1H), 7.96 (dd, 1H), 7.20-6.80 (m, 9H), 3.37 (m, 3H), 2.68 (m, 1H), 2.41 (m, 1H), 1.67 (s, 6H), 1.33 (m, 2H), 0.77 (t, 3H). LC-MS: m/e 554 $(M + H)^+$ (4.6 min).

EXAMPLE 18



N'-[1-(3-Chlorophenyl)-2-(4-chlorophenyl)ethyl]-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide

To a mixture of N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-allyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide (Example 11, 150 mg, 0.27 mmol), acetic acid (0.062 mL, 1.08 mmol), and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) in 2 mL of dichloromethane was added phenylsilane (0.066 mL, 0.54 mmol). After stirring at rt for 5 h, the reaction was quenched with triethyl amine (0.2 mL), and the resulting mixture loaded onto a silica column eluting with 10-40% EtOAc in hexanes to afford the title compound. ^1H NMR (500 MHz, CD_3OD): δ 8.23 (bd, 1H), 7.82 (dd, 1H), 7.22 (m, 1H), 7.15 (d, 2H), 7.11 (m, 2H), 6.98 (m, 1H), 6.95 (d, 2H), 6.83 (d, 1H), 4.18 (dd, 3H), 2.95 (dd, 1H), 2.76 (dd, 1H), 1.58 (s, 3H), 1.56 (s, 3H). LC-MS: m/e 512 $(M + H)^+$ (4.5 min).

BIOLOGICAL EXAMPLE 1

Cannabinoid Receptor-1 (CB1) Binding Assay.

Binding affinity determination is based on recombinant human CB1 receptor expressed in Chinese Hamster Ovary (CHO) cells (Felder et al, Mol. Pharmacol. 48: 443-450, 1995). Total assay volume is 250 µL (240 µL CB1 receptor membrane solution plus 5 µL test compound solution plus 5 µL [3H]CP-55940 solution). Final concentration of [3H]CP-55940 is 0.6 nM. Binding buffer contains

50mM Tris-HCl, pH7.4, 2.5 mM EDTA, 5mM $MgCl_2$, 0.5mg/mL fatty acid free bovine serum albumin and protease inhibitors (Cat#P8340, from Sigma). To initiate the binding reaction, 5 µL of radioligand solution is added, the mixture is incubated with gentle shaking on a shaker for 1.5 hours at 30°C. The binding is terminated by using 96-well harvester and filtering through GF/C filter presoaked in 0.05% polyethylenimine. The bound radiolabel is quantitated using scintillation counter. Apparent binding affinities for various compounds are calculated from IC_{50} values (DeBlasi et al., Trends Pharmacol Sci 10: 227-229, 1989).

The binding assay for CB2 receptor is done similarly with recombinant human CB2 receptor expressed in CHO cells.

The compounds, found in Examples 1-18 were tested in the above assay and found to have an IC_{50} value of 2 micromolar or less.

Selective CB1 antagonist/inverse agonist compounds have IC_{50}s 100-fold greater in the CB2 binding assay than in the CB1 assay, and generally have IC_{50}s of greater than one micromolar in the CB2 binding assay.

BIOLOGICAL EXAMPLE 2

Cannabinoid Receptor-1 (CB1) Functional Activity Assay.

The functional activation of CB1 receptor is based on recombinant human CB1 receptor expressed in CHO cells (Felder et al, Mol. Pharmacol. 48: 443-450, 1995). To determine the agonist activity or inverse agonist activity of any test compound, 50 µL of CB1-CHO cell suspension are mixed with test compound and 70 uL assay buffer containing 0.34 mM 3-isobutyl-1-methylxanthine and 5.1 µM of forskolin in 96-well plates. The assay buffer is comprised of Earle's Balanced Salt Solution supplemented with 5 mM $MgCl_2$, 1 mM glutamine, 10 mM HEPES, and 1 mg/mL bovine serum albumin. The mixture is incubated at room temperature for 30 minutes, and terminated by adding 30µl/well of 0.5M HCl. The total intracellular cAMP level is quantitated using the New England Nuclear Flashplate and cAMP radioimmunoassay kit.

To determine the antagonist activity of test compound, the reaction mixture also contains 0.5 nM of the agonist CP55940, and the reversal of the CP55940 effect is quantitated. Alternatively, a series of dose response curves for CP55940 is performed with increasing concentration of the test compound in each of the dose response curves.

The functional assay for the CB2 receptor is done similarly with recombinant human CB2 receptor expressed in CHO cells.

CB1 antagonist/inverse agonist compounds of the present invention generally have EC_{50}s of less than 1 micromolar in the CB1 functional assay and selective CB1 antagonist/inverse agonists have generally have EC_{50}s of greater than 1 micromolar in the CB2 functional assay.

BIOLOGICAL EXAMPLE 3

Acute food intake studies in rats or mice: General Procedure

Adult rats or mice are used in these studies. After at least 2 days of acclimation to the vivarium conditions (controlled humidity and temperature, lights on for 12 hours out of 24 hours) food is removed from rodent cages. Experimental compounds or their vehicles are administered orally, intraperitoneally, subcutaneously or intravenously before the return of a known amount of food to cage. The optimal interval between dosing and food presentation is based on the half-life of the compound based on when brain concentrations of the compound is the highest. Food remaining is measured at several intervals. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant effect of the compounds are compared to the effect of vehicle. In these experiments many strains of mouse or rat, and several standard rodent chows can be used.

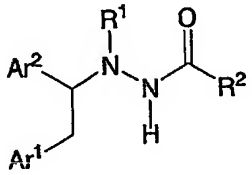
BIOLOGICAL EXAMPLE 4

Chronic weight reduction studies in rats or mice: General Procedure

Adult rats or mice are used in these studies. Upon or soon after weaning, rats or mice are made obese due to exclusive access to diets containing fat and sucrose in higher proportions than in the control diet. The rat strains commonly used include the Sprague Dawley bred through Charles River Laboratories. Although several mouse strains may be used, c57Bl/6 mice are more prone to obesity and hyperinsulinemia than other strains. Common diets used to induce obesity include: Research Diets D12266B (32% fat) or D12451 (45% fat) and BioServ S3282 (60% fat). The rodents ingest chow until they are significantly heavier and have a higher proportion of body fat than control diet rats, often 9 weeks. The rodents receive injections (1 to 4 per day) or continuous infusions of experimental compounds or their vehicles either orally, intraperitoneally, subcutaneously or intravenously. Food intake and body weights are measured daily or more frequently. Food intake is calculated as grams of food eaten per gram of body weight within each time interval and the appetite-suppressant and weight loss effects of the compounds are compared to the effects of vehicle.

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 is selected from:

(1) hydrogen,
(2) C_{1-4}alkyl,
(3) C_{3-6}cycloalkyl,
(4) C_{2-4}alkenyl, and
(5) C_{2-4}alkynyl;

R^2 is selected from:

(1) C_{1-10}alkyl,
(2) C_{2-10}alkenyl,
(3) C_{2-10}alkynyl,
(4) C_{3-10}cycloalkyl,
(5) C_{3-10}cycloalkyl C_{1-4}alkyl,
(6) cycloheteroalkyl,
(7) cycloheteroalkyl C_{1-4}alkyl
(8) aryl,
(9) aryl C_{1-10}alkyl,
(10) aryl C_{2-8}alkenyl,
(11) diaryl C_{1-4}alkyl,
(12) heteroaryl,
(13) heteroaryl C_{1-10}alkyl,
(14) NR^cR^d,

wherein each alkyl, alkenyl, and alkynyl is straight or branched chain and unsubstituted or substituted with one to four substituents independently selected from R^a and each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^b;

Ar^1 and Ar^2 are independently selected from:

(1) aryl, and
(2) heteroaryl,

wherein aryl and heteroaryl are unsubstituted or substituted with one to four substituents independently selected from R^b;

each R^a is independently selected from:

(1) -OR^d,
(2) -$NR^cS(O)_mR^d$,
(3) halogen,
(4) -SR^d,
(5) –$S(O)mR^d$,
(6) -$S(O)_mNR^cR^d$,
(7) -NR^cR^d,
(8) -$C(O)R^d$,
(9) -CO_2R^d,
(10) -CN,
(11) -$C(O)NR^cR^d$,
(12) -$NR^cC(O)R^d$,
(13) -$NR^cC(O)OR^d$,
(14) -$NR^cC(O)NR^cR^d$,
(15) -CF_3, and
(16) -OCF_3;

each R^b is independently selected from:

(1) R^a,
(2) C_{1-10}alkyl,
(3) oxo,
(4) aryl,
(5) arylC_{1-4}alkyl,
(6) heteroaryl, and
(7) heteroarylC_{1-4}alkyl;

each R^c and R^d is independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) C_{2-10} alkenyl,
(4) cycloalkyl,
(5) cycloalkyl-C_{1-10}alkyl,
(6) cycloheteroalkyl,
(7) cycloheteroalkyl-C_{1-10} alkyl,
(8) aryl,
(9) heteroaryl,

(10) pyridyl,
(11) pyrimidyl,
(12) aryl-C_{1-10}alkyl, and
(13) heteroaryl-C_{1-10}alkyl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-R^g,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;
each R^g is independently selected from:
(1) hydrogen,
(2) C_{1-4}alkyl,
(3) -C(O)C_{1-4}alkyl,
(4) –C(O)OR^d,
(5) –C(O)NR^cR^d,
(6) –$S(O)_mR^d$, and
(7) -$S(O)_mNR^cR^d$;
each R^h is independently selected from:
(1) halogen,
(2) C_{1-10}alkyl,
(3) -O-C_{1-4}alkyl,
(4) -S-C_{1-4}alkyl,
(5) -$S(O)_m$-C_{1-4}alkyl,
(6) -CN,
(7) -NO_2,
(8) -CF_3,
(9) -CHF_2 and
(10) -OCF_3; and
m is selected from 1 and 2.

2. The compound according to Claim 1, wherein:
Ar^1 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three R^b substituents; and
Ar^2 is selected from: phenyl, and pyridyl, wherein phenyl and pyridyl are unsubstituted or substituted with one to three R^b substituents,
and pharmaceutically acceptable salts thereof.

3. The compound according to Claim 2, wherein:

Ar^1 is para-chlorophenyl and Ar^2 is selected from: m-chlorophenyl, m-bromophenyl, and m-cyanophenyl,
and pharmaceutically acceptable salts thereof.

4. The compound according to Claim 1, wherein:
R^1 is selected from:
(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) propyl, and
(5) allyl,
and pharmaceutically acceptable salts thereof.

5. The compound according to Claim 1, wherein:
R^2 is selected from:
(1) C_{1-8} alkyl,
(2) C_{3-6} cycloalkyl,
(3) cycloheteroalkyl,
(4) phenyl,
(5) phenyl C_{1-3} alkyl,
(6) pyridyl,
(7) pyrimidyl,
(8) pyridyl C_{1-3} alkyl, and
(9) pyrimidyl C_{1-3} alkyl,
wherein each alkyl moiety is straight or branched chain and unsubstituted or substituted with one, two or three substituents independently selected from R^a, and each cycloalkyl, cycloheteroalkyl, phenyl, and heteroaryl moiety is unsubstituted or substituted with one, two or three substituents independently selected from R^b;
each R^b is independently selected from:
(1) $-OR^d$,
(2) halogen,
(3) -CN,
(4) $-CF_3$,
(5) $-OCF_3$,
(6) cycloheteroalkyl;
(7) C_{1-4}alkyl,
(8) oxo,

(9) phenyl,
(10) benzyl, and
(11) heteroaryl;

each R^d is independently selected from:

(1) hydrogen,
(2) C_{1-5}alkyl,
(3) $-CH_2CH=CH_2$,
(4) cyclohexyl,
(5) cyclopentyl,
(6) cyclopropyl,
(7) cyclobutylmethyl,
(8) cyclopentylmethyl,
(9) cyclohexylmethyl,
(10) pyrrolidinyl,
(11) phenyl,
(12) thiazolyl,
(13) pyridyl,
(14) pyrimidyl,
(15) benzothiazolyl,
(16) benzoxazolyl,
(17) triazolyl,
(18) benzyl, and
(19) pyridyl-methyl-,

wherein each R^d may be unsubstituted or substituted with one to three substituents selected from R^h;

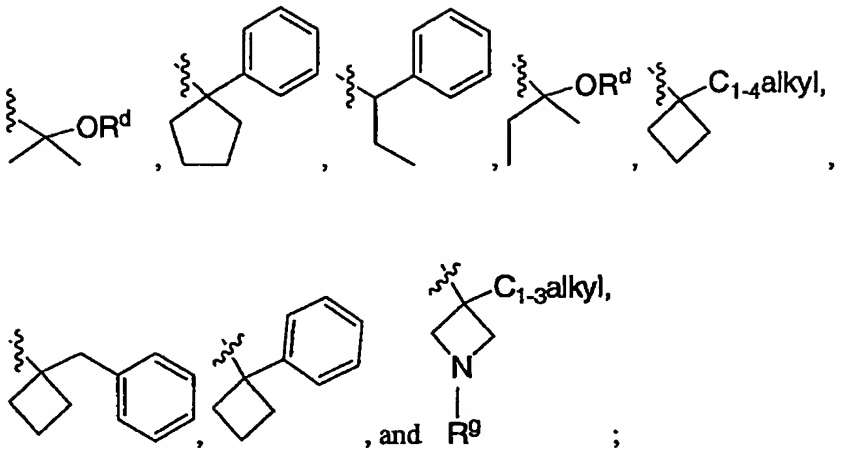
each R^h is independently selected from:

(1) halogen,
(2) methyl,
(3) methoxy,
(4) $-S(O)_m-C_{1-4}$alkyl,
(5) -CN,
(6) $-CF_3$,
(7) $-CHF_2$, and
(8) $-OCF_3$;

and pharmaceutically acceptable salts thereof.

6. The compound according to Claim 1, wherein:

R^2 is selected from:



each R^d is independently selected from:

(1) hydrogen,

(2) phenyl,

(3) pyridyl, and

(4) pyrimidyl,

wherein phenyl, pyridyl and pyrimidyl are unsubstituted or substituted with one or two R^h substituents; and

each Rg is independently selected from:

(1) hydrogen,

(2) C_{1-4}alkyl;

and pharmaceutically acceptable salts thererof.

7. The compound according to Claim 1, selected from the group consisting of:

(1) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[5-(trifluoromethylpyridin-2-yl)oxy]propanoyl}hydrazide;

(2) N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide;

(3) N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(1-phenylcyclopentanecarboxyl)hydrazide;

(4) N'-[1-(3-bromophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide;

(5) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide;

(6) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-[5-trifluoromethypyridin-2-yl)oxy]butanoyl}hydrazide;

(7) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-allyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide;

(8) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(2-methyl-2-hydroxypropanoyl)hydrazide;

(9) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-(2-methyl-2-hydroxypropanoyl)hydrazide;

(10) N'-[1-(3-cyanophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-{2-methyl-2-[(5-trifluoromethylpyridin-2-yl)oxy]propanoyl}hydrazide;

(11) N'-[1-(3-cyanophenyl)-2-(4-chlorophenyl)ethyl]-N'-methyl-N-[(2S)-phenylbutanoyl]hydrazide;

(12) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N'-propyl-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide; and

(13) N'-[1-(3-chlorophenyl)-2-(4-chlorophenyl)ethyl]-N-{2-methyl-2-[5-trifluoromethypyridin-2-yl)oxy]propanoyl}hydrazide;

and pharmaceutically acceptable salts thereof.

8. The use of a compound according to Claim 1 for the manufacture of a medicament useful for treating a disease mediated by the Cannabinoid-1 receptor.

9. The use according to Claim 12, wherein the disease mediated by the Cannabinoid-1 receptor is selected from: psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders, cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders relating to opiates, alcohol, marijuana, and nicotine; constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, and obesity or other eating disorders associated with excessive food intake.

10. The use of a compound according to Claim 1, for the manufacture of a medicament useful for the treatment of obesity.

11. The use of a compound according to Claim 1 for the manufacture of a medicament useful for treating a disease mediated by the Cannabinoid-1 receptor.

12. The use according to Claim 11, wherein the disease mediated by the Cannabinoid-1 receptor is selected from: psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders, cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders relating to opiates,

alcohol, marijuana, and nicotine; constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, and obesity or other eating disorders associated with excessive food intake.

13. The use of a compound according to Claim 1, for the manufacture of a medicament useful for the treatment of obesity.

14. The use of a compound according to Claim 1 for the manufacture of a medicament for the prevention of obesity in a person at risk therefor.

15. A composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

16. The composition according to Claim 15 additionally comprising an HMG-CoA reductase inhibitor.

17. The composition according to Claim 15 additional comprising 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, or a pharmaceutically acceptable salt thereof.